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THE ROLE OF THE PITUITARY POSTERIOR HORMONE IN FAT METABOLISM

W. RAAB, M.D.

PRAGUE, VIENNA

Many authors [Bailey and Bremer (1), Camus and Roussy (2) and others] deny any importance of the hypophysis for the physiological regulation of fat metabolism and for the development of obesity since the symptoms that are frequently ascribed to pathological changes of the hypophysis can be fully reproduced by experimental injury of the base of the midbrain and especially of the tuber cinereum. The work of Cushing (3) and Biedl (4) and others suggests, however, that there is a very close relationship between the pars intermedia and posterior lobe of the hypophysis and the mesencephalon not only in local but also in functional respect. Biedl assumes a stimulating action of the middle and posterior lobe hormone upon certain metabolism centers in the midbrain.

A long series of experiments that I (5) have carried out in dogs shows that pituitrin regularly exerts a definite effect upon the fat content of the blood. While the blood fat (petrol-ether-fraction) usually rises during fasting, pituitrin causes on the contrary a fall which, as it has also been shown by Blix and Ohlin (6), is due to a diminution or even complete disappearance of the circulating neutral fat. This reaction lasts for several hours and the normal level is reattained within about twenty-four hours. Doses of several cubic centimeters are needed to produce the effect if given by subcutaneous injection, while much smaller amounts (about 1/10 of the subcutaneous doses) are fully effective if injected into the brain ventricles, thus demonstrating the local action of pituitrin in the midbrain. The pituitrin effect disappears after mechanical destruction of the tuber cinereum or after administration of drugs that paralyze the mesencephalic centers (pyramidon, antipyrin, aspirin). It is also absent after transection of the cervical spinal cord, after section of the abdominal splanchnic and after paralyzing the sympathetic nervous system with ergotamin. The depressant action of pituitrin upon the phospholipoids of the blood [Blix and Ohlin (6)] I have recently found to be lacking or at least weakened in Professor Cannon's completely sympathectomized dogs (5c).

Various authors [Coope and Chamberlain (7), Oshima (8), Steppuhn and collaborators (9)] have observed an accumulation of fat in the liver following injection of pituitrin, which also lasts for several hours and then disappears again. At the same time the peripheral tissue fat diminishes temporarily [Steppuhn and collaborators (9)].

A survey of these experimental facts gives clear evidence that the pituitrin posterior lobe hormone has doubtlessly a definite influence upon fat metabolism and it seems justified to draw the conclusion that pituitrin favors the absorption of circulating fat by the liver by a nervous path starting in the tuber cinereum and ending in the liver. If one assumes a certain quantity of fat to be thus normally destroyed within the liver tissue it is evident that any disturbance in the cooperative activity of the "pituitary mesencephalic system" will leave these fat amounts undestroyed. They will be stored in the tissues and consequently lead to obesity.

There is a striking parallelism between the mechanism of the so-called chemical heat regulation and the mechanism of the action of pituitrin in fat metabolism. Both of them have their nervous center in the tuber cinereum, both of them are abolished by antipyretic drugs acting upon these centers, both of them are abolished by section of the cervical spinal cord [Freund and Grafe (10)] and abolished or weakened by sympathectomy [Cannon (11)] and by ergotamin [Rigler and Silberstern (12)]. Hypophysectomy damages the heat production; this can be restored, however, by the administration of pituitrin [Hashimoto (13)]. Subjects of pituitary obesity frequently have a lowered body temperature [Cushing (14)]. It seems, therefore, not impossible that the physiological significance of the action of pituitrin would be an intrahepatic oxydation of fat contributing to the maintenance of heat production.

As an illustration of the possibility of development of obesity by pure pituitary lesion there might be mentioned a case that I observed in Professor Biedl's Clinic in Prague. A male patient, 31 years old, was healthy until two weeks before admission. Within this latter time headaches, loss of sexual potency, and sudden rapid development of obesity in the face, on the abdomen and on the hips was noted. An increase in weight of ten kgm. occurred. The abdominal skin showed large dark reddish striae each about three inches wide. There was a slight erosion of the anterior wall of the sella. There were eye symptoms. The patient died a few weeks later of septicemia deriving from a phlegmon. The hypophysis was macroscopically scarcely enlarged. Histologically there was found, however, a very small basophile adenoma which had almost entirely taken the place of the posterior lobe. The neighboring nervous regions were intact. This case of an "acute" pituitary obesity is perhaps the only one described in which any participation of the tuber cinereum, etc., can be ruled out with certainty.

On the other hand, there are known cases of purely mesencephalic

obesity caused by encephalitis, tumors, hydrocephalus, etc., without any lesion of the hypophysis.

Any attempts to treat cases of this latter kind with pituitrin must fail because of injury and inactivity of the responding nervous organ. Also in purely hypophyseal or other cases of obesity one cannot expect any considerable therapeutic effect of pituitrin since the subcutaneous route offers no possibility of contact with the midbrain tissue in effective concentration, while the adequate intracranial way is not, of course, suitable for a continuous treatment. Besides, pituitrin does not seem to remove fat after it is once deposited in the tissue stores. A comparison of the arterial and venous fat content of the limbs does not show a definite mobilizing effect of pituitrin [Raab (5)].

I want to emphasize the remarkable parallelisms between the adrenosympathetic and the pituitary-mesencephalic systems. In both we see a mutual cooperation of an endocrine "gland" which as a matter of fact is not a real gland but an organ deriving from nervous tissue and acting through its hormone specifically upon its respective nervous mother-tissue. In both cases there is a local and probably also functional relationship with a neighboring real glandular structure: the adrenal cortex and the pituitary anterior lobe. Both hormones, adrenalin and pituitrin, show a series of similar actions on the vascular system and on smooth muscle, both of them influence metabolism and heat regulation apparently in a definite way.

SUMMARY

Large subcutaneous or smaller intraventricular doses of pituitrin decrease the neutral fat content of the blood. The reaction is abolished by mechanical destruction or pharmacological paralysis of the centers in the tuber cinereum, after transection of the spinal cord, after paralysis or section of the abdominal splanchnic, or after paralyzing the latter with ergotamine, or after phosphorus poisoning. An accumulation of fat in the liver and a decrease of the peripheral tissue fat has been noted after pituitrin injection. The conclusion is drawn that pituitrin promotes the absorption and destruction of circulating fat by the liver through a nervous pathway starting in the tuber cinereum and running through the cervical spinal cord and the abdominal splanchnic to the liver. Any disturbance of the cooperative pituitary-mesencephalic system would lead to a retention of excess fat amounts in the body and thus lead to obesity. Comparative arterio-venous fat determinations suggest that pituitrin does not affect deposit fat directly. There seems to be a close relationship between the pituitrin-nervous mechanism for fat destruction and the so-called chemical heat regulation. Verified cases of purely hypophyseal and purely mesencephalic obesity have been observed by the author.

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ESTROGENIC SUBSTANCES. II. AN ANALYSIS OF PLANT SOURCES

BURNHAM S. WALKER, Ph.D. and JAMES C. JANNEY, M.D., F.A.C.S.

From the Evans Memorial and Boston University School of Medicine
BOSTON

An interesting by-product of the study of the female sex hormones was the observation that substances capable of initiating estrus in the castrated female mouse could be obtained from certain plant tissues as well as from the reproductive and other tissues of animals.

Following the introduction by Allen and Doisy (1923) of the vaginal smear method of testing for the presence of estrogenic material, Loewe, Lange and Spohr (1927) investigated several flowering plants, with positive results. Fellner (1926) reported an active extract from grains of rice and wheat. Using their chromaphil reaction as a test method, in addition to uterine growth and the vaginal smear, Dohrn, Faure, Poll and Blotevogel (1926) obtained positive results with a group of plant materials, including beet seeds, potatoes and yeast. Glimm and Wadehn (1928) made a thorough investigation of yeast extracts, from both brewer's and compressed yeast, with positive results. In his recent monograph, Frank (1929) notes a positive extract obtained from cooked potatoes. With extracts of tomato juice and of bacterial cultures (B. coli and B. pyocyaneus) he obtained (in collaboration with Goldberger and Gustavson) strictly negative results.

This present study was begun with the intention simply to study a variety of plants and plant products with respect to their content in estrogenic material. During the course of the study we have been able to observe certain indications of a relationship between estrogenicity and the portion of a plant used as a source of extract, and also with the age of the plant tissue in question and the rate of its growth.

Our extracts were prepared by one or the other of two type procedures: alcohol extraction and chloroform extraction.

Alcohol extraction was carried out by allowing the fresh material to stand covered with 95 per cent alcohol for a period of several days at room temperature. The liquid was then pressed from the solid portions and evaporated to small volume. Cheese-cloth was used to strain out the solid material; filter paper is not advisable on account of its tendency to adsorb the active material (Laqueur, Hart and de Jongh, 1926). The sludge remaining after evaporation of the alcohol was made alkaline with sodium carbonate and extracted with ether. (With material which tended to emulsify with ether sufficient anhydrous sodium carbonate was added to take up all the water.) The residue remaining after evaporation of the ether was taken up in physiological salt solution and injected. (In a few

cases where the residue was distinctly oily, oil of sesame was used as the injection vehicle.)

Chloroform extraction was carried out in the tissue extractor described in our previous communication (Janney and Walker, 1930). The chloroform was then separated from the solid material, evaporated and the residue treated with alkali and extracted with ether as described above. The remainder of the procedure was the same as for the alcohol extract.

The technique of the mouse tests was the same as used by us heretofore and described in previous papers (Janney, 1929; Janney and Walker, 1930).

The majority of the plant materials proved negative when their extracts were injected into castrated white mice. The negative results are summarized briefly in Table I.

TABLE I

Material	Type of Extraction	Maximum Number of Grams of Original Tissue per Dose	Number of Mice Used
Apples	Alcohol	200	6
Beets	Alcohol	200	8
Cabbage	Alcohol	500	10
Carrots	Alcohol	500	5
Carrots (young)	Chloroform	300	10
Corn	Alcohol	500	6
Grapes	Alcohol	500	5
Peaches	Alcohol	500	6
Plums	Alcohol	500	6
Potatoes	Alcohol	200	12
Spinach	Chloroform	200	20
Sweet Potatoes	Alcohol	500	6
Swiss Chard	Chloroform	200	24
Tomatoes	Alcohol	133	6

In the experiments summarized above, the materials were in all cases (except the young carrots) mature and obtained from market or garden in the form usually sold for food purposes. The tops were removed from the root vegetables, the corn was cut from the cob, the peaches and plums were stoned before weighing. Weights refer to fresh tissue before extraction.

In addition to the above plant extracts, solutions or suspensions of certain plant constituents were injected and found negative. The substances so tested were carotin, chlorophyll, inositol, phytin, saponin and urson.

A certain limited number of experiments, on the other hand, yielded definitely positive results.

Alder leaves and catkins. These were collected in early spring and extracted with alcohol. Male and female catkins were collected and extracted separately. The leaves of the alder were also collected at the same time and extracted.

Willow catkins. These were collected later in the season and extracted with alcohol, male and female catkins separately. A small percentage of positive reactions was observed.

Sprouted oats. The oil obtained by chloroform extraction of 20 grams of oats after sprouting was sufficient to initiate estrus in a castrated mouse. The oil from 100 grams of unsprouted oats failed to bring about any reaction.

Rhubarb leaves. Collected in May. Extracted with chloroform. Positive reactions with large doses.

The more detailed experimental results with these positively reacting extracts are given in Table II.

TABLE II

Material	Grams Original Tissue per Dose	Number of Mice	Number Positive	Number Negative
Alder Catkins.....(male).....	160	1	1	0
	80	3	3	0
	20	1	1	0
(female).....	20	3	3	0
Alder Leaves.....	30	6	3	3
	20	1	1	0
Willow Catkins.....(male).....	50	1	1	0
	20	5	0	5
(female).....	20	5	1	4
	12	1	1	0
Oats.....(unsprouted)....	150	12	4	8
	100	6	0	6
(sprouted).....	100	4	4	0
	50	4	4	0
	25	4	4	0
	20	2	2	0
	10	2	0	2
Rhubarb Leaves.....	200	4	4	0
	100	5	3	2

(Smaller doses all negative.)

From the above results it appears that a relatively high concentration of estrogenic material occurs in plants:

1. Associated with green pigmentation. Roots or tubers of plants were in our experiments strictly negative (contrast Dohrn, Faure, Poll and Blotevogel, 1926). Even young growing roots were negative, as shown by the chloroform extract of very small carrots, which was negative in amounts corresponding to 300 grams. Fruits were entirely negative. The presence of estrogenic material in yeast (Glimm and Wadehn, 1928) should be mentioned as an outstanding exception to this generalization.

2. Coincidently with rapid growth. Green parts of plants which had passed the phase of rapid growth were also negative (see Table I). All

the positive extracts were obtained from plants in the early spring when growth is most rapid, except in the case of the sprouted oats, where a similar condition of rapid growth was artificially induced.

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RECENT OBSERVATIONS ON THE IODINE REACTION IN EXOPHTHALMIC GOITER*

WILLARD OWEN THOMPSON AND PHEBE K. THOMPSON
From the Department of Medicine, Rush Medical College,
and
The Presbyterian Hospital
CHICAGO

Our observations may be summarized under three main headings:

1. The range of effective iodine dosage.
2. Refractoriness to iodine.
3. Prolonged treatment by iodine alone.
4. Myxedema during the administration of iodine.

THE DOSE OF IODINE

While working in the thyroid clinic of the Massachusetts General Hospital in Boston, we made an attempt to determine the smallest dose of iodine that will produce any reduction in basal metabolism and the smallest amount that will produce a maximum reduction. For this purpose we observed the effect on basal metabolism of the daily administration of about 6 mgms.† of iodine (roughly, one drop of the compound solution), 3 mgms., 1.5 mgms. and 0.75 mgm. to four series of hospital patients with exophthalmic goiter and compared the effect with that of much larger doses given initially (1) (2) (3) (4). The routine was to wait until a stationary level of basal metabolism was reached. Compound solution of iodine in one of the doses mentioned was then administered and daily observations of the metabolism were made. When the metabolism again reached a level, much larger doses (usually 30 minims daily) were given and their effects noted.

The reduction in basal metabolism during the daily administration of 6 mgms. of iodine appeared to be as great as that noted by Starr, Segall and Means (5) in the same clinic, during the daily administration of about 126 mgms. (roughly, 1 cc. of the compound solution).

During the daily administration of 6 mgms., 88 per cent of the cases showed a reduction in basal metabolism of 10 or more points; during the daily administration of 3 mgms., 65 per cent; during the daily administration of 1.5 mgms., 50 per cent; and during the daily administration of 0.75 mgm., 33 per cent.

The average response in the 6 mgm. series was 27 points (from plus 46 to plus 19 per cent); in the 3 mgm. series it was 14 points (from plus 40 to plus 26 per cent); in the 1.5 mgm. series it was 9 points (from plus 43

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†The amounts of iodine recorded in this article are approximate, owing to the rough method of measurement (1).

to plus 34 per cent); and in the 0.75 mgm. series it was 4 points (from plus 39 to plus 35 per cent).

Between a daily dose of 0.75 mgm. of iodine and one of 6 mgms., the relation between the percentage approach of the basal metabolism towards the normal level and the daily dose of iodine appeared to be roughly a straight line.

The dose of compound solution of iodine commonly employed in the treatment of exophthalmic goiter is about 30 to 45 minims daily, roughly, 250 to 375 mgms. of iodine. Compared with this, 6 mgms. a day might appear too small a dose to be effective. However, compared with the normal rate of iodine utilization, it is large. Boothby et al. (6) have shown that the basal metabolic rate of a "thyroidless individual" may be maintained at a standard normal level by an average daily intravenous dose of 0.25 mgm. of thyroxin, an amount which contains 0.16 mgm. of iodine. From Boothby's observations, it follows that the normal thyroid gland probably does not elaborate thyroxin at a rate faster than 0.25 mgm. daily, and there are reasons for believing that the actual rate may be less than this. (7). Moreover, from analyses of various foods, it seems probable that most people with normal thyroid glands do not ingest as much iodine as this. Thus 6 mgms. of iodine roughly represents at least 35 times the amount which is daily broken down by a normal gland in the form of thyroxin.

We wish to make it clear, however, that this dose is not recommended for the routine preoperative and postoperative treatment of exophthalmic goiter. We have observed patients who failed to show a maximum response to this dose initially, and have seen patients in whom more was required to produce a maximum effect as refractoriness to iodine was developing. Just what the largest dose that is ever required to produce a maximum effect may be, has not been determined. That it is much less than the 30 to 45 minims of the compound solution commonly employed in the routine treatment of the disease appears probable. Certain observations suggest that it is not more than 30 mgms. a day (roughly, 5 drops of the compound solution) (1) (2) (3). For the present, it is our impression that a dose at least this large should be used in the routine treatment of the disease. We know of no contraindications to much larger doses except their unpleasant taste and occasional gastro-intestinal disturbances.

A question that naturally arises is whether the minimum amount of iodine that will produce a maximum reduction in basal metabolism is any different in a goitrous area from that in Boston, a non-goitrous area. In an attempt to solve this problem we have begun a study of the disease in Chicago. Thus far, two patients have shown a well marked reduction in basal metabolism during the administration of 6 mgms. daily and one subject, no response either to 6 mgms. or to 250 mgms. daily administered immediately afterwards. While there may prove to be a difference between the two regions, it would seem that this difference is not likely to be a striking one.

The data also suggest that sufficient iodine must be administered in a sufficiently short time for a maximum storage of colloid to occur. It appeared from the figures of Marine and Lenhart (8), Wilson and Kendall (9), Weir (10) and Cattell (11) that 6 mgms. a day might be just about adequate for this result if most of it could be used for the storage of colloid, whereas the smaller doses were inadequate to cause a maximum storage of colloid in the time that the maximum metabolic effects were noted (3) (4). There was thus observed a rough parallelism between the amount of iodine available for storage of colloid and the percentage approach of the basal metabolism towards the normal level.

In five patients the reaction to iodine was a reversible one, the daily administration of about 0.75 mgm. to 3 mgms. of iodine being associated with an increase in basal metabolism and the severity of the disease, and the immediate subsequent daily administration of about 250 mgms. being associated with a decrease in both factors. These observations suggest that, in certain cases, if the amount of iodine administered falls below a certain amount, it may be used by the thyroid to form a still greater excess of thyroxin; whereas, if the iodine intake exceeds a certain amount, it reverses the reaction and causes a decrease of the thyroxin output. This finding is of interest in connection with the observation that patients with non-toxic goiter may begin to suffer from thyrotoxicosis during the ingestion of such small quantities of iodine as those contained in iodized salt.

It appears from this study that a dose of iodine which in itself may be too small to cause any reduction in basal metabolism (e. g., 1.5 mgms. daily) may, in some way, interfere with the effect of much larger doses (250 mgms. daily) administered immediately afterward. This effect was not as striking in the 3 mgm. series and could not be said to have been produced by the daily administration of 0.75 mgm. Whether the amount of iodine in iodized salt is ever sufficient to produce this effect is unknown. In any event, from the standpoint of the routine preoperative treatment of the disease, it would seem desirable to give initially a sufficient amount of iodine to produce the maximum beneficial effects.

REFRACTORINESS TO IODINE

Patients may be initially refractory to iodine or may become refractory during its prolonged administration, after showing an initial response.* The first type of response is probably less common than the second. When patients are refractory, all the peculiar nervous manifestations of the disease are usually marked and the operative risk may be great. If a patient becomes refractory after showing an initial response, omission of iodine for four weeks or longer may be accompanied by the disappearance of the refractoriness. Iodine may then be readministered and operation performed with safety. When the metabolism is rising rapidly during the administration of iodine, it seems to us always wise to

*Examples of the development of refractoriness are recorded elsewhere (1).

omit iodine and postpone operation. During this period, the patient should be at rest in bed in the hospital. In patients who are initially refractory to iodine the details of treatment have not been worked out.

PROLONGED TREATMENT BY IODINE

The response of patients with exophthalmic goiter to iodine is variable, and temporary improvement is not to be considered the only result of long continued medication. While at the Massachusetts General Hospital, we (12) observed the effect of administering iodine for long periods to 24 patients (14 with mild and 10 with severe or moderately severe cases) who had not been otherwise treated. With three exceptions (all unsatisfactory responses to iodine), the patients pursued their daily work throughout the period of observation, thus eliminating the effect of rest. In 9 of the 14 mild cases (64 per cent) the results were satisfactory, i. e., the clinical evidence of thyrotoxicosis was either completely or almost entirely kept under control, and the basal metabolism was kept at a normal level. In 4 of these 9 cases, in which iodine was omitted from ten to sixteeen months, the disease had apparently disappeared; and in 3 others, in which iodine had been omitted from four to seventeen weeks, there had been no recurrence of symptoms. In 3 of the 14 mild cases (22 per cent) the results were fairly satisfactory, i. e., there was definite improvement in spite of tardiness or fluctuations in the response. In two mild cases (14 per cent) the results were unsatisfactory. In the 10 severe or moderately severe cases, the results were satisfactory in one (10 per cent); there was no permanent satisfactory benefit in 4 (40 per cent); and the disease became worse in 5 (50 per cent).

At the same clinic we (13) observed the effect of administering iodine for long periods to 27 patients who were thyrotoxic following a subtotal thyroidectomy for exophthalmic goiter. In 3 of these patients little or no reduction of basal metabolism was noted during its administration, and in 3 others, only a temporary reduction. In 18 of the remaining 21 cases the basal metabolism could be held at a more or less constant level for months to years by continuous administration. In 11 of these the level to which iodine thus depressed the metabolism was plus 15 per cent or lower; in 6, plus 16 to plus 20 per cent; and in one case, plus 21 to plus 25 per cent. In 3 cases, the level to which iodine depressed the metabolism was somewhat inconstant and ranged between 0 and plus 33 per cent. In all cases showing only temporary improvement or none at all during the administration of iodine, there was a large amount of palpable thyroid tissue.

These observations suggest that the most important thing in determining the response of patients with exophthalmic goiter to prolonged iodine medication may be the severity of the disease, mild cases commonly responding satisfactorily and moderately severe and severe cases rarely showing more than temporary improvement.

MYXEDEMA DURING THE ADMINISTRATION OF IODINE

During the administration of iodine to a patient whose basal metabolism is standard normal following a subtotal thyroidectomy for exophthalmic goiter, any one of the following effects may be noted:

1. No response—the most common result.

2. Depression of the basal metabolism to a subnormal level without any accompanying clinical evidence of underfunction of the thyroid gland (14).

3. Depression of the basal metabolism to a subnormal level, in association with the development of myxedema (15) (16).

The latter two types of response are occasionally seen in mild untreated cases of exophthalmic goiter. The third type of response is rare, and so far we have noted it in only three cases following operation and in only two preceding operation. In these patients 1.5 to 4.5 months elapsed from the time the iodine was started until the basal metabolism dropped from a standard normal level to its lowest point and myxedema developed. The myxedema could be made to disappear either by omitting iodine or by continuing iodine and giving thyroid in addition. Both procedures produced the same clinical picture. The development of myxedema during iodine administration is not confined to the immediate postoperative period, but may occur years after operation. The patients who developed myxedema following operation appeared to be in a healthy state when their basal metabolism was normal and they were not receiving iodine. A diminution in heat production has occasionally been produced by administering iodine to patients who have never suffered from exophthalmic goiter (17) (18) and to normal animals (19) (20) (21).

Thus, so far as can be determined clinically, the myxedema which occasionally develops during the administration of iodine to patients who have a normal basal metabolic rate following a subtotal thyroidectomy for exophthalmic goiter, is due to an inhibition of the secretion of the normal thyroid hormone. This suggests that iodine may cause a reduction in the high basal metabolism of exophthalmic goiter in the same manner.

SUMMARY

In Boston the smallest amount of iodine that will produce any reduction in basal metabolism in exophthalmic goiter is greater than 0.75 mgm. daily in about two-thirds of the cases. The minimum amount that will produce a maximum reduction is roughly 6 mgms. daily in the majority of cases. Between these two limits, the relation between the percentage approach of the basal metabolism towards the normal level and the size of the dose is roughly linear. The effective dose has not been determined in Chicago, but it is known that 6 mgms. a day will cause a marked reduction in basal metabolism in some cases.

Iodine must be administered at a certain minimum rate in order for the maximum effects to be produced. It also appears that this rate may be one that is sufficient to cause colloid to be stored at an adequate rate.

In a few cases the reaction to iodine is reversible.

The administration of a small dose such as 1.5 mgms. daily may sometimes interfere with the effect of a much larger dose administered immediately afterward.

In the routine treatment of the disease, it is desirable to give initially an excess of iodine sufficient to produce maximum effects. The amount necessary to do this is undetermined, but probably is not more than 30 mgms. (roughly 5 drops of the compound solution) daily.

In patients who develop refractoriness to iodine, it is wise to postpone operation until iodine has been omitted long enough to allow the refractoriness to disappear.

In a large percentage of mild cases of the disease improvement may be maintained for long periods by iodine, whereas moderately severe or severe cases rarely show more than temporary improvement.

Myxedema may occasionally develop during the administration of iodine to patients who have a normal basal metabolism following subtotal thyroidectomy for exophthalmic goiter and to patients with mild untreated cases of the disease.

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THE EFFECT OF ANTERIOR PITUITARY EXTRACT ON THE DEVELOPING ALBINO MOUSE*

GEORGE EDWIN JOHNSON AND ROBERT TOWNER HILL
Kansas State Agricultural College
MANHATTAN, KANSAS

INTRODUCTION

The present paper extends anterior pituitary injection work in this laboratory with rats (1) to mice, and stresses the effect upon the male genital system. The work of Evans and associates (2, 3, 4, 5, 6) on rats, of Robertson and Ray (7) on mice, and of Putnam, Teel and Benedict (8) on rats and dogs have shown a stimulation of growth from injected extracts of this gland. Similar influences have also been indicated by other work on hypophysectomized rats (9, 10, 11), on thyroidectomized rats (12), and on castrated rats (13, 14). Evans and Long (2, 3) reported inhibition of oestrus and excessive lutein formation in female rats from such injections and similar results have been obtained by Johnson and Sayles (1). Stimulation of sexual development on the other hand has been produced by transplant methods (9, 15, 16, 17) and by extracts prepared from urine of pregnant women (18, 19, 20). Fertility in male rats appeared at first not to be affected by anterior pituitary injections (21) but later work indicated a loss of sexual interest in such rats (5, 19). Engle (22), however, showed enlargement of sex organs, except testes, of male rats which had been injected with the urine of pregnant women.

METHODS

The extract used in the experiments reported here was prepared from the anterior lobes of bovine pituitary glands obtained cold from Kansas City, according to the method given by Johnson and Sayles (1). Essentially this consists of an extraction with sodium hydroxide with a later neutralization by acetic acid, followed by filtering.

The young mice were weaned at the age of 20 days, and as nearly as possible half of the animals of each sex were taken as "experimentals" (injected with extract) and the remaining ones were taken as controls (injected with 0.9 per cent saline solution). Injections of 0.1 cc. were made for each of the first five days. If the animals grew well the dose was increased 0.1 cc. every five days until a maximum of 0.5 cc. was injected daily. Weights were taken at five day intervals.

In general, the earlier animals used were injected for 130 days and killed at 150 days of age. In order to learn at what period of life the extract caused changes in size and histological appearance, if any, of the

*Contribution No. 131 from the Department of Zoology, Kansas State Agricultural Experiment Station, Manhattan, Kansas.

TABLE I

Effect of Anterior Pituitary Extract on Weight of Female Mice

Days of Age	20	30	40	50	60	70	80	90	100	110	120	130	140	150
Average Weight of Experimental Females in Grams	6.7	11.0	14.3	17.6	20.1	21.2	22.7	24.5	25.3	26.0	26.8	26.2	26.5	26.4
Average Grams Heavier than Controls[1]	—0.9	—0.2	0.5	1.5+	1.1+	1.4+	1.5+	3.1—	3.1—	2.3+	2.2	2.0	1.9+	2.4
Number of Experimentals[2]	33	33	30	27	24	21	20	18	16	14	11	9	8	8
Number of Controls	24	24	21	19	17	15	15	14	12	10	9	7	6	5
Per Cent of Experimentals Heavier than Littermate Controls[3]	3	45	60	78	67 (75)	71	80	94	100	86 (93)	82 (91)	89	88	88

[1]—A plus (+) after a figure indicates that that figure would be greater if corrections were made on account of temporary incerases in weight produced by pregnancy. A minus (—) indicates the opposite. A minus (—) before a figure indicates that the figure has a negative value.
[2]—The number of animals decreases with age in Tables I and III because they were killed at different ages for histological study.
[3]—Figures in parentheses give the percentage after corrections are made for temporary weight changes produced by pregnancy.

gonads of both sexes, other animals were killed to give a series from 30 to 150 days of age. Bouin's fluid was used for fixing and Ehrlich's hematoxylin for staining. Measurements were made of the ovaries; testes; body from the tip of the nose to the base of the tail, and from the base to the tip of the tail; and the right hind leg from the anterior edge of the acetabulum to the end of the longest toe. The testes and ovaries were also measured for length, width and thickness and relative volumes roughly computed by multiplying the three dimensions.

The mice were raised from some kindly provided by the Laboratory of Mammalian Genetics of the University of Michigan. Since these mice had been inbred for many generations, less variation would be expected than in a mixed population. Animals of a litter were usually kept in one cage, or sometimes in adjoining cages. All cages were kept under like conditions. Precautions were taken to keep the mice free from internal parasites through cleanliness and by using food which contained no insect intermediate hosts for tapeworms. With two exceptions all the animals were found to be free from internal worm parasites and no external parasites were noticed.

RESULTS AND DISCUSSION

Growth of Female

Results. Tables I and II give the pertinent data for females with respect to body weight and body measurements. A study of Table I, and of the original weights which were taken at five day intervals shows that the weights of the anterior pituitary injected females rose from below that of the controls, between 35 and 45 days of age, becoming distinctly higher at 50 days. At 70 days the average difference was 1.42 gm., all females being considered, which, however, is not a statistically significant difference. If those females which had been pregnant at any time during the experiment are eliminated, the difference is 2.16 gm., which is significant (D/PE=4.9). At 150 days the experimentals were 2.4 gm. heavier than the controls, a difference which is hardly significant (D/PE=3.1), but when animal 2—4, which had been pregnant three times, is omitted the difference in weight, 3.30 gm., is significant (D/PE=5.9).

The increased growth of the experimental females took place over the entire body. Table II shows that the experimentals generally had greater

TABLE II

MEASUREMENTS OF EXPERIMENTAL FEMALE MICE AND COMPARISONS WITH CONTROLS

	Body	Tail	Hind Leg
Average length of all experimental females in mm...	97.2	78.7	31.9
Average greater length as compared with controls in mm.....	3.8	0.0	0.4
Number of experimental females longer than controls	17	12	11
Same lengths as controls.....	0	0	2
Shorter than controls.....	4	7	8
D/E.....	4.2	1.7	1.0

TABLE III

EFFECT OF ANTERIOR PITUITARY EXTRACT ON WEIGHT OF MALE MICE

Days of Age	20	30	40	50	60	70	80	90	100	110	120	130	140	150
Average Weight of Experimental Males in Grams	7.0	11.5	15.3	18.8	21.4	22.2	23.7	24.7	25.2	25.2	26.1	23.0	23.4	23.0
Average Grams Heavier than Controls	—0.6	—0.3	0.1	0.5	1.3	1.4	1.9	1.7	2.5	1.8	2.3	— 0.1	0.9	1.0
Number of Experimentals	26	26	23	20	18	14	12	11	8	4	3	2	2	2
Number of Controls	25	25	23	20	18	14	12	10	7	4	3	2	2	2
Per Cent of Experimentals Heavier than Littermate Controls	0	62	70	70	78	86	83	73	88	75	100	50	100	100

bone dimensions than the controls. Only the increase in body length, however, appears significant. It was usually more clearly seen in older animals.

Discussion. The results showing a moderate increase in growth from the injection are similar to those reported by Johnson and Sayles (1) in the albino rat. The lack of extreme giantism, such as was obtained in rats by Evans (23), may be due partly to the fact that the experiments reported here terminated at 150 days or less and partly to Evans' use of an extract prepared by centrifugation which may have been more potent for production of growth.

Growth of Males

Results. The weights and body measurements of the males included in this study are given in Tables III and IV. At the beginning of the experiment the experimentals averaged 0.6 gms. lighter than those selected for controls, but at the age of 38 days, they averaged more in weight and continued so to the end of the experiment. At the age of 70 days the injected males averaged 1.42 gm. heavier than the controls, a difference which is not statistically significant (D/PE=2.4). At 90 days of age the experimentals were 2.3 gm. heavier than the controls, a difference which approaches significance (D/PE=3.17). The figures show a decided increase in growth of the experimental males from the age of 70 to 90 days.

TABLE IV

MEASUREMENTS OF EXPERIMENTAL MALE MICE AND COMPARISONS WITH CONTROLS

	Body	Tail	Hind Leg
Average length of all experimental males in mm....	92.8	78.4	31.7
Average greater length as compared with controls in mm.....	3.5	0.8	0.9
Number of experimental males longer than controls	15	10	12
Same length as controls.....	0	2	2
Shorter than controls.....	3	6	4
D/E.....	4.3	1.4	2.8

The increase in growth, however, was not as great as in the females. The marked growth at the age of 150 days suggests that the gains may be greater than that of the females late in life. However, the number of males left at the end of the experiment was too small to support a valid conclusion as to this point. As in the case of the females the growth in the experimental males took place over the body and was not limited to the skeleton as shown in Table IV. The differences, however, are small and scarcely significant except for body length, as was the case for the females.

Discussion. The present work on male mice confirms the results of Johnson and Sayles (1) with rats. While statistical treatment for any single period does not show the increased growth of either treated male mice or rats to be clearly significant, the fact that the general trend is in that direction, that both experiments showed a positive difference, and the fact that the treated females were significantly heavier than their controls

supplies strong evidence for the belief that the results were not due to chance. This conclusion is supported by the fact that the experimentals were lighter in weight than the controls at first and by the fact that almost without exception they were heavier than their controls after 50 days of age, making the weights at any one age less likely to be produced by chance. It should be noted that Smith and Engle (15, 16) also found that the male rat responded less to anterior pituitary transplants than did female rats, but Evans and Simpson (5) state that males become giants as well as females with their centrifuged extract. The question arises as to whether the growth response of the male is less than that of the female because of the activity of the testes in the male. Would castration permit it to make a more decided response? Evans and Simpson (6) have indicated that the castrated injected male does not gain as rapidly as the normal injected male rat.

Effect on Female Genital System

Results. In both experimental and control females the ovaries appeared to be very similar at the ages of 31, 35, 41 and 50 days, containing many follicles of varying stages but no corpora lutea in all of the six experimentals and in four of five controls. One control 41 days old had a well developed corpus luteum. The chief difference noted was that in the injected animals there was less tendency to form follicular cavities than in the controls. In the medium-sized follicles cavity formation might be absent and in the larger follicles the cavity would usually not be so large as in the controls, indicating the tendency for follicles to change to corpora lutea without the occurrence of ovulation. Corpora lutea were present in the ovaries of three females (two experimental and one control) killed at 55 days of age. They were numerous in the two experimentals but few in number in the control. There were practically as many follicles in the experimentals as in the controls.

In 22 extract-injected females from 65 to 150 days of age, the ovary contained a very large number of corpora lutea and in the older animals it often had a diameter three times as great as that of the ovary of the saline-injected control. There was only one experimental animal which had a small number of large corpora lutea characteristic of the normal or control animal of these ages. This animal was pregnant and therefore contained the small number of corpora lutea of pregnancy. A control female 105 and one 150 days old had no corpora lutea. The corpora lutea of the controls had more definite boundaries than many of those of the experimentals, especially where the latter were small and numerous. In animals 65 days or more of age a much smaller proportion of the ovary consisted of follicles in the injected animals than in the controls, but because of the great enlargement of the ovary there was no consistent difference in the actual number of follicles in the entire ovary, judging from counts in one ovary each of six experimentals and of four controls and a general study of the others. Considerable variation was found in both groups.

Not only did the histological evidence indicate that many ova were hemmed in by lutein cells before the follicle could rupture and ovulation take place, but the records show that only four pregnancies (see Table I, 1-1, 6-2, 14-1) were produced in the 28 injected animals that reached the age of 50 days or more. From these there was a total of three mice born; four normal embryos were removed from one female at autopsy, and in another female four embryos, apparently normal, were found at autopsy to be partly resorbed. In the 19 control females, 50 or more days old, there were nine pregnancies and two abortions.

In the study of the ovary slides several ova were discovered in a fallopian tube. This led to a careful study and restudy of the tubes by the senior author and Mr. Richard R. Marsh. Fortunately, the tubes were found present on usually two to four slides of the ovary for nearly all of the females 50 or more days old. Of the 20 experimentals with tubes one to 12 or 23 tubal ova were found in 13 animals, or a total of 88 or 66 tubal ova, depending on whether we include 22 peculiar eggs that appeared more or less vacuolated, shrunken and flattened occurring in one tube. Of the 14 control animals with tubes from three to five tubal ova were found in four animals, or a total of 18 tubal ova. Of the experimentals, therefore, 65 per cent had tubal ova, but only 28 per cent of the controls had them. Tubal ova averaged 4.4 (or 3.3 if the 22 abnormal ova are eliminated) per animal in the 20 experimentals, but only 1.3 in the 14 controls.

The ages at which sacrificed experimentals showed tubal ova were as follows (each number in parentheses indicates the number of ova in one animal): 40 days (5 ova); 70 days (5); 80 days (5); 90 days (12, 5); 100 days (8); 110 days (22); 130 days (9); and 150 days (1, 3, 3, 3, and 10). For the controls the ages and tubal ova were: 80 days (5 ova); 90 days (5); 130 days (5); and 150 days (3).

Discussion. The present work shows that in the mouse, as in rats and some other animals considered by others, the formation of lutein bodies is greatly stimulated by anterior pituitary extract such as has been used. Somewhat similar results were obtained with an acid-extracted substance from the anterior pituitary by Larson, Bergeim, Barber and Fisher (24). They suggest that their result might have been produced by the protein content of their extract. The extract used in the present study, however, produced not only lutein formation but in a few cases permitted the formation of normal follicles and ovulation followed by normal pregnancy. More particularly it should be noted that it produced a larger number of tubal ova than were present in the controls. This result can hardly be attributed to some incidental inclusion, but rather to a hormone in the extract. It appears possible, however, that the growth hormone at least is associated with the protein portion of an alkaline extract, for Evans' protein rich centrifuged extract produced more growth than our filtered extract. The fact that both excess lutein formation and increased ovulation giving groups of tubal ova resembling those shown by Smith and Engle (16) were produced by the extract would indicate that our extract contained not

only growth hormone but also the maturity producing hormone usually demonstrated by transplants.

In not showing production of oestrus in immature rats our experiments agree in general with those of Bellerby (25) but not with those of Teel (26), who claimed to have produced oestrus with alkaline extracts.

Effect on the Male Genital System

Results: The size of the testes was not greatly affected by the anterior pituitary extract. Nine experimental animals had larger and eleven had smaller testes (relative combined volume of both testes) than the respective controls. Of these experimentals only three had testes more than 50 cu. mm. (0. 05 cc.) larger and only five had testes more than this amount smaller than their respective controls. The total relative volumes of the testes of the experimental animals averaged about 54 cu. mm. (0.054 cc.) smaller than those of the controls. In general these results indicate a slight reduction in size of testes as a result of anterior pituitary injections.

TABLE V

PREGNANCY OCCURRING IN CONTROL FEMALES MATED WITH NORMAL AND WITH ANTERIOR PITUITARY TREATED MALES

Mated with Normal Males				Mated with Treated Males		
Saline Injected Females	Age in Days When With Normal Males	Number of Days	Times Pregnant	Age in Days When With Injected Males	Number of Days	Times Pregnant With Injected Males
1—1	45—115	70	2	—	—	—
2—4	45—150	105	3	—	—	—
3—4	45— 80	35	0	—	—	—
6—4	45— 92	47	0	92—120	28	0
6—5	45— 92	47	0	—	—	—
12—3	45— 62	17	1	62—149	87	*1
13—5	45— 57	12	1	57—110	53	0
14—2	45—120	75	1	—	—	—
17—6	45— 68	23	0	68— 95	27	0
18—6	45— 63	18	**1	63— 90	27	0
20—7	45— 65	20	1	—	—	—
Totals.....	.....	469	10		222	1
Average number of days for each pregnancy.....		46.9			222	

*Five embryos aborted at half term.
**One embryo aborted at about sixteen days.

The breeding records as given in Table V show a high degree of sterility in the experimental males, since only one pregnancy (five embryos aborted at half term) was produced and this required 222 days as compared with the normal of one litter produced in every 46.9 days.

At autopsy the testes of six of the experimental animals (ages 60, 62, 80, 92, 150 and 150 days) appeared to contain within the membrane surrounding the entire mass of tubules a deposit resembling calcareous material, such as a very thin or "soft" shell abnormally appearing on hen eggs. By probing with a needle this membrane could be broken, but, as it was apparently laid down in the membrane, pieces of it could not be picked off as from a hen's egg. Histological examination later confirmed

the autopsy record and added another male (2-3) of 150 days as having this hardened membrane and also a similar material in one of the tubules. Those testicular membranes which had been recorded as appearing hardened were found to have different staining properties than the normal membranes, taking on a deep blue in the younger animals and a pronounced lavender in the older animals. This coloration appeared first in the membrane at its inner or near its inner surface and progressed outward or in both directions especially in the inner half of the tunica albuginea. This tissue normally was fibrous with elongated nuclei. In intermediate stages of taking up the blue coloration the nuclei appeared to be drying up. In later stages of such deposits all the nuclei had disappeared, leaving a fibrous sheath which stained lavender with hematoxylin and eosin which were the stains used on most of the sections. The very outer layer of the tunica albuginea remained cellular. In four experimental animals (one at 80 and three at 150 days of age) a similar hardening occurred also in some of the tubules. In the animal at 80 days the tubules of one testis were entirely replaced by this hard material and were surrounded with a great amount of connective tissue instead of the usual small amount of interstitial tissue.

There were other histological differences between the testes of the experimental and control males, but since they did not appear to be consistent the slides were restudied by both authors and by Mr. Nelson Wade. In eight of the 25 experimentals there appeared to be more interstitial tissue in the testes than in their controls, and more than the controls in general in the case of 12-2 and 17-1, which had no littermate controls. In the other cases the amounts were essentially alike. The eight which appeared to have more interstitial tissue were 35, 50, 60, 72, 80, 115, 150, and 150 days old when killed. The increased amount of interstitial tissue was usually associated with increased amount of connective tissue around the tubules and with hardening of the testicular wall, and the latter condition was often associated with reduced size in the testes.

Little difference was seen in the Cowper's glands of the experimental and control animals, except in the case of 1-2, in which one Cowper's gland contained a large internal mass of colloid of a volume equal to about one-half of the surrounding secreting tissue, which had fewer nuclei than normal. Cowper's glands of the other experimentals and of the controls had varying amounts of colloid, especially in a tract leading to the duct of the gland. In this were scattered nuclei, indicating the breaking down of cells. There appeared to be more colloid and disintegration of cells in some of the experimentals than in their controls.

Discussion: A larger amount of interstitial tissue in the testes of injected animals indicates the presence, in the extract which was used, of the same principle which Engle (22) employed in his experiments on rats with urine from pregnant women. As in his experiments there was no increased spermatogenesis in the present case and the injected animals showed more indication of disintegration of seminal epithelium than did

the controls. Also as in Engle's experiments there was found slightly smaller testes in the injected animals than in the controls, but the difference was not constant nor marked.

The present experiment shows that the extract used greatly reduces the fertility of male mice, confirming the findings of Evans and Simpson (5) that treated male rats showed a loss of sex interest, and of Johnson and Sayles (1) that treated male rats showed some but not complete sterility. The results differ somewhat in this regard from those of Crofts and Flower (21) who found repeated instances of fertile males following months of daily injections. Differences in extracts, dosage and species would probably account for the divergence in results.

The present work indicates histological changes primarily in the testes, but sometimes in Cowper's glands, which probably partly account for the sterility, though it is not clear just how these changes produce the sterility. The cause may, of course, be physiological, resulting from the histological changes reported above.

SUMMARY

The daily injection of bovine anterior pituitary extract (alkaline, later neutralized and filtered) into 21 female and 14 male albino mice produced at 70 days of age an increase in growth over that of 11 control females and 14 control males, which were injected with physiological salt solution. This increase was more marked in the females than in the males.

The extract produced a marked increase in the size of the ovaries after the age of 55 days through excessive lutein body formation and persistence. Only one experimental female had a normal ovary with the few corpora lutea associated with normal function, and this was a pregnant animal. Increased lutein formation was associated with a high degree of sterility, but apparently also with an excess number of tubal ova. None of the control females had an excessive number of corpora lutea.

In the injected male mice seven showed a hardening of the testicular wall. Some showed an increase in interstitial tissue and there was some destruction of seminal epithelium. Excess colloid was formed in some of the Cowper's glands. The experimental male mice showed a very high degree of sterility compared to the normal males.

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THE STIMULATIVE EFFECT OF ROENTGEN RAYS UPON THE GLANDS OF INTERNAL SECRETION*

A Review of the Literature.

MURRAY B. GORDON, M.D.
From the Endocrine Clinic, Department of Pediatrics,
Long Island College Hospital
BROOKLYN, N. Y.

Arndt in explanation of experiments with medicinal drugs, expounded the following as a biological concept: "Weak stimuli accelerate vital processes, moderate promote them, strong inhibit them and strongest destroy them" "[Kleine (schwache) Reize fachen die Lebenstatikeit an, mittle starke forden sie, starke hemmen sie, und starkste heben sie auf]." This hypothesis was elaborated by Schultz in 1899 into what now is known as the Arndt-Schultz Law. It has since been extended to serve as the basis for stimulative radiation and also as the main point of difference between the various investigators in this field.

The very wording of the hypothesis has given rise to contentions as to its proper meaning, the term stimulus especially being the cause of controversial discussion. Holzknecht and Pordes consider that the word itself is ambiguous and vague and that it is used in a different sense from that embraced in the expression "stimulative effect." According to Dejardins, stimulation in the physiological sense occurs whenever any reaction takes place between two bodies and is capable of producing a positive or negative response. Stimulation, then, does not necessarily mean that the reaction must be a positive one: it may be constructive or destructive, but the generally accepted meaning in the literature is that of a positive, constructive effect.

If by stimulation is implied an increase in cellular growth or activity, whether permanent or transitory, x-ray stimulation may theoretically act in one of three ways: (1) It may directly cause an intracellular change in the functioning cells resulting in an increased function or growth; (2) it may indirectly stimulate by causing degeneration of the surrounding cells and removing their inhibiting influence; (3) degeneration of the latter cells may liberate chemical substances which stimulate the functional cells to increased activity.

These diametrically opposed interpretations have resulted in the formation of two main schools of investigators, both conceding that functional activity may follow small dose radiation but differing radically in the conception of the biological processes involved. Manfred Fraenkel

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heads the group which claims that small doses actually stimulate by direct biopositive action of the rays. Holzknecht and Pordes are the protagonists of those who absolutely deny the possibility of any stimulating effect without simultaneous destruction. X-rays always destroy, the degree of destruction being in direct ratio to the amount of radiation. Their interpretation of the increased cellular activity resulting from small doses is not that of a direct stimulative action but that of a depressing factor which frees the cells from a restraining influence.

No attempt will be made in this presentation to review the thousands of experiments which have been performed in an endeavor to correlate the effects of cellular radiation with the Arndt-Schultz law. These investigations have been carried out on unicellular organisms, plants, seeds, vegetations, micro-organisms and on members of the animal kingdom. It has been demonstrated by numerous observers that under certain conditions the tenets of this law are valid. Some of the biological effects which have been observed as a result of weak irradiations may now be discussed.

Acceleration in growth of germinating seeds may be induced (Koernicke and Gager). Radiated buds may show an increase in growth (Molisch). In radiated root tips the number of mitoses may be increased. Bohn effected the first stage of parthenogenetic development through radiation. The rest period of winter buds may be shortened through radiation (Weber). Radiation of sugar cane may not only bring about acceleration of growth but also produce an increase in sugar content. Richards and Packard have accelerated the first stages of segmentation of ova. Lazarus-Barlow and Bektoen experimented with ova of Ascaris megalocephala and found that small doses of radiation produced increased cellular division and that heavier doses or more prolonged radiation diminished the rate of division. Gutzeit, Brinkmann and Katschau also were able to demonstrate stimulation by small dose radiation on micro-organisms. Marcus obtained an increase in multiplication of paramecia in cultures. Gillman as well as Baetjer and Congdon noted increased development of eggs in amphibia and birds which was followed by retardation and malformation. Hoffmann observed that radiation in small doses both accelerated and advanced the development of tadpoles. Weak radiation may stimulate the growth of newly born mice and may hasten opening of the eyes (P. Lazarus). Suguira and Failla also noted an increased rapidity of growth in mice with small dose radiation and injurious effects with larger amounts.

Halbertstaedter and Simons conclude from their experiments on horse beans that small doses of x-rays stimulate living tissue and that the stimulating period is preceded by a latent stage which is inversely proportionate in duration to the ray sensitiveness of the cell and the strength of the radiation. This inert interval is considered by some to be due to transitory injurious effect on a particularly sensitive cytoplasm which is followed by an increased compensatory growth (Hirsch). Increased metabolic processes have been observed by several investigators. Redfield and Bright found that low intensities of radiation stimulated cells and tissues

to increased metabolism as evidenced by greater production of carbon dioxide. Barreto, on exposing canaries to small doses, obtained an increased rate of oxygen consumption. Leo Loeb noted an increase in metabolism following small dose radiation.

Numerous investigators have failed to obtain these so-called stimulative effects following irradiation in small dosage. Schwarz, Czepa and Schindler did not succeed in obtaining a constant growth promotion in their thousands of experiments on plants (oats, wheat, beans) but on the contrary observed such variability of results that their original belief in the stimulative effect was changed. They concluded that the so-called stimulative effects of weak intensities of radiation could be explained on the basis of fluctuations in temperature and moisture.

That positive results are transitory and cannot be maintained beyond narrow limits is the contention of Dejardins based upon the experiments of Arntzen and Krebs upon germinating peas. These latter investigators observed that growth promotion was limited to the initial 24 to 48 hours after irradiations, diminishing steadily thereafter.

Frik and Kruger found that the roentgen rays which definitely injured the reproductive capacity of Bacillus prodigiosus were not capable of increasing this capacity in doses down to 1/3500 of the injury dose.

In 1923, Ivy, McCarthy and Orndorff presented evidence showing that the submaxillary and gastric glands are not stimulated by small doses of radiation. Orndorff, Farrell and Ivy later noted that 1/10 H.E.D. radiation over the pancreas increased the concentration of lipase and trypsin but did not affect the quantity of the secretion. This group of investigators do not accept the Arndt-Schultz phenomenon as applicable to the action of x-rays on glandular activity.

The experiments with poisons performed by Schultz and upon which the Arndt-Schultz law was confirmed have been repeated by others who have failed to obtain, however, confirmatory results. Zeller, Heubner, Joachimoglu and Meier all report negative findings.

Pordes reviewed the pharmacological literature on the applicability of this law in that field and reports that there is no Arndt-Schultz law to the pharmacologist. He claims that many medicinal remedies always paralyze and includes in this class strychnine, curare and cocaine, denying a stimulative effect in the smallest dose.

Because of the fundamental differences in conditions resident in the unicellular organism and in the human body, it is felt by many that the entire concept of growth promotion in plants is not equivalent to that obtaining in the complex human body. The value of experimental investigations in the laboratory is minimized when an attempt is made to apply the results to man (Colwell and Russ, Ewing, Hirsch, Dejardins).

These introductory remarks on small dose radiation outside of the human body have been included for purposes of orientation. In general, one may accept for the purpose of this paper Kotschau's dictum that the Arndt-Schultz phenomenon depends upon the following conditions:

(1) the dose; (2) the effective agent used; (3) the object upon which the experiment is performed; (4) the irritability of the organ in reference to the effective agent; (5) the medium in which the organ or organs are contained; (6) the functional state of the organ at the moment of conducting the experiments. The applicability of these conditions to radiation therapy will be noted in the effects of the x-rays on cellular protoplasm in general and on the endocrine glands in particular.

Cellular protoplasm is susceptible to radiation but the various cells differ in their susceptibility. According to the law of Bergonie and Tribondeau, the more embryonal or undifferentiated the type of cell, the greater is its radio-sensitivity, and conversely the more differentiated and highly specialized the cell, the greater is its resistance.

Cells in mitosis and which are growing are more reactive than those in a resting state. Those containing large amounts of chromatin are more easily acted upon. The endothelial lining of blood vessels is extremely sensitive to both radium and roentgen rays, so that cells having a richer blood supply react more readily than those with a scantier one. The cells of some tissues are affected much more by a given dose of irradiation than are those of another. According to Wolf, the radio-sensitivity of the endocrine glands in the order of their susceptibility is as follows: Adrenal, thyroid, ovary, pituitary, testes, parathyroid.

There is no absolute measure for cellular sensitivity. Normal radiosensitivity of both tissue and skin is fairly constant and is utilized in determining the dosage of radiation, but that of pathological tissue is so variable and is dependent upon so many factors that it cannot be brought into relationship to skin reactions.

The unit of dosage utilizes the reaction of the skin to a certain quantity of radiation administered. Holzknecht in 1902 advanced the precept that when a definite dose of x-rays is administered to a healthy skin there ensues a definite latent period followed by a definite stage of reaction which commences gradually, rises to maximum and then subsides. The larger the dose, the shorter the latent period, the greater the reaction and its duration. Numerous units of dosage have since been advocated but they all are arbitrary and give a varying degree of clinical value. The term H.E.D. signifies Hauteinheitsdose and is sometimes designated as S.E.D., skin erythema dose. It is unfortunate that the doses mentioned in the literature are not standardized, as this interferes with a proper evaluation of the results for purposes of comparison.

The terms small, moderate or large doses are also arbitrary and their use in some instances makes comparison almost impossible. There does not seem to be any definite idea as to just what is meant by a small dose, especially when used in connection with a so-called stimulative effect. To illustrate the difference of opinion and the added difficulty involved in evaluating results, Hirsch advocates the following arbitrary scale of doses: Destructive dose, 100 per cent; inhibitive dose, 75 per cent; stimulating dose, 25 to 35 per cent. In contradistinction to this, the majority of work-

ers in this field consider a stimulative dose to be between 5 and 10 per cent H.E.D. with 20 per cent perhaps as the upper limit. A skin erythema dose should not be confused with a castration dose. It is outside the province of this review to consider in detail the various units of dosage or the action of various wave lengths of radiation.

In his first publication Schultz claimed that a weakened organ is more susceptible to the action of drugs than a normal one. This has been extended by those who accept his law to include the effects of radiation. Fraenkel in various laboratory and clinical studies claims to have demonstrated that tissues and organs which in a physiological state cannot be influenced by x-rays, become more sensitive when they are in a pathological condition. This claim is denied by Dejardins and others.

The necessary requisite for radiation therapy directed against any endocrine gland is primarily a knowledge of the underlying existing disease, but unfortunately this is not always possible at the present time with endocrine disorders. This uncertainty has resulted in the use of the term dysfunction instead of the designation of either hyper- or hypo-function, as the case may be. At best, therefore, any present endocrine treatment must be empirical. The glands which have been irradiated for therapeutic purposes and the indications are: ovary, for the regulation of the menstrual cycle in amenorrhea, dysmenorrhea, oligomenorrhea, and for the cure of sterility; pancreas, to alleviate diabetes mellitus; adrenal, to increase functional activity in Addison's disease and other states of hypoadrenalism; pituitary, to correct certain gynecological conditions, to stimulate the gland in dystrophia adiposo-genitalis and to cure impaired hearing; thymus, for its indirect effect on psoriasis; thyroid, for mental improvement in children, and for direct effect on certain skin conditions.

The pioneer in small dose radiation was Leopold Freund of Vienna, who administered it for conditions of the skin and hair. According to Holzknecht, his interpretations of the effect were erroneous since he based them upon an electrical foundation, but his observations of increased functional activity were correct.

Stimulative endocrine radiation was introduced in 1913 by Manfred Fraenkel, who found that by applying a fraction of the dose required to abolish ovarian function, he was able to induce regulation of the menstrual cycle in amenorrhea and hypomenorrhea. His method, the so-called "Reizbestrahlungen," has since been made use of by numerous gynecologists and roentgenologists and is today one of the accepted procedures in the treatment of certain gynecological conditions.

OVARY

The results of small dose radiations in gynecological conditions are open to the interpretations of cellular stimulation in general. If normal regular menstruation and fertility are evidences of physiological ovarian function, then any aberration from the normal may be accepted as symptoms of an impaired function, with certain reservations which will be cov-

ered later in the paper. Fraenkel and his school claim that the beneficial results of ovarian radiation are due directly to stimulation and are evidenced in a local hyperemia of the ovary, an increased cellular nutrition and an increased functional activity. Some, like Thaler, also include a general hyperemia of the entire female generative system and of the intestinal lymphatics among the end results of weak irradiation. Others attribute a biphasic function to the ovary: the production of ova and the hormonic function, each residing in a different set of cells with an individual radio-sensitiveness. Steinach claims that the dose of x-rays which will destroy the follicular apparatus causing amenorrhea will stimulate the so-called interstitial cells or female puberty gland.

Holzknecht and Borak, on the other hand, contend that radiation in small doses produces a disintegration of ova and of those follicles which are in a diseased or weakened condition, while the healthy functioning cells remain. Due to loss of the disturbing element, the result is one of increased functional activity.

Menstrual disorders are either essential, where the etiological factor resides in the generative system, or symptomatic where the underlying cause is to be sought in constitutional disease. In the latter type, ovarian radiation is of course only a palliative measure. In some instances ovarian radiation is contraindicated, Hirsch including among these tuberculosis, syphilis, pernicious anemia, nephritis, adnexal disease, cystic ovarian tumors and genital tumor.

In polymenorrhea, where the cause lies in follicular changes and in ovarian hypofunction, the results have been fair, according to Seitz and Wieloch, while Wolf has been able to obtain an increase in menstrual flow in some cases. In the absence of other etiological factors, endocrine imbalance is to be considered in dysmenorrhea and radiation attempted, even though the results may not always be successful.

The best results have been obtained in treatment of amenorrhea. Seitz distinguishes between primary amenorrhea, where menstruation has never appeared, and secondary, where it has ceased after having been present. Unfortunately a proper evaluation of the merits of radiation in each type is unobtainable, as the majority of authors do not designate the type present in their patients. According to Seitz, the poorest results are those in the treatment of primary amenorrhea. This author has collected from the literature 239 cases of amenorrhea which were treated by small dosage radiation of the ovaries. Measuring the effects of treatment by return to normal menstrual cycle, his analysis shows that 118 (about 50 per cent) were cured, 14 improved, and 28 failed to react. Pregnancy subsequently occurred in 30 (13 per cent). On the basis of these results, he concludes that there must exist a relationship between radiation, regulation of menstruation and the subsequent pregnancy.

Seitz's statistics cover the reports of Thaler, Flatau, Sippel, Von Rooy, Caufman, Gal, Heimann, Wagner and Schonhof, Wieloch and himself.

Thaler reported good results in functional diseases of the ovary, based upon the treatment of 147 women, 62 of whom were included in Seitz's analysis. The effects were noted in a few weeks after the institution of treatment. He feels that a patient who does not show any improvement after two or three exposures should not obtain any further treatment.

Flatau in several communications reports success with this type of treatment in women who had failed to improve with previous organotherapy. In 21 cases of sterility, due to hypoplastic or asthenic anomaly of the ovaries, pregnancy subsequently occurred in 12, eight of these being carried to term. He feels that radiation in small doses is an efficient type of therapy in ovarian infantilism, and advises that the field of radiation should include the entire ligamentous apparatus with its nerves and vessels, as well as the uterus and ovaries.

Wieloch believes that the less capable an ovary is of functioning properly, the more difficult it is to effect a favorable result and the smaller dose required to paralyze its function.

Heimann in a later report states that he obtained good results in two-thirds of his cases, two of the women conceiving in 3 to 4 months subsequent to treatment and being delivered of normal, healthy infants. He does not mention the number of cases under observation nor the dosage administered.

Recasens noted that the treatment of dysmenorrhea by radiation in virgins was not as satisfactory as in married women, due in some instances to insufficient development of the anterior uterine wall, which produced an anterior flexion and dysmenorrhea. He used a 20 per cent erythema dose, but he does not mention the number of cases under observation or the percentage of cures.

Drips and Ford, from study of the literature, conclude that there is enough clinical evidence showing favorable regulation of menstruation and subsequent full term delivery of normal infants in women who were formerly sterile to justify its use in carefully selected cases.

In 36 patients with ovarian dysfunction treated by Hirsch, 22 improved, while 14 failed to show any benefit; conception ensued in 7. He administered doses ranging from 1/10 to 1/20 H.E.D., or 15 per cent castration dose, with slight variations, depending upon the age of the patient, the duration of the condition, and the thickness of the abdominal wall. In reviewing his failures, he found that they were due to the following conditions: Congenital maldevelopment of the entire genital tract, pelvic inflammation, sterility and sexual frigidity, beginning fibrosis of the uterus, with probably a like condition of the ovaries and age, two of the patients being above 36 years old. He refers to Linzenmeier, who observed pregnancy occurring after ovarian radiation in a woman who had a fibroid tumor of the uterus. Thaler is also of the opinion that age of the patient is a factor in the outcome of ovarian treatment by x-rays.

There are others, too numerous to mention, who have obtained good clinical results by irradiation of the ovaries in gynecological disorders. Some radiate the ovaries only, while others include the entire lower abdomen and pelvis.

Experimental studies on animals have been undertaken to determine the type of changes produced by small dose irradiation. Geller, on radiating young rats and rabbits, found no alteration in the cells with 5 per cent erythema dose, but with 10 and 20 per cent H.E.D. there were evidences of degeneration noted in both ova and follicles in all stages without manifestations or predilection for ripe follicles.

His results are not considered applicable to the situation in women, as he studied young animals who had not yet attained puberty. Podljaschuk repeated the experiments but used both young and mature rabbits, i. e., those which had ripe follicles. He found that doses of 25 to 45 per cent H.E.D. did not show any stimulative changes.

Wagner and Schonhof feel that the results obtained in the experiments of Geller cannot be carried over to the mature woman. They selected young women who were to undergo panhysterectomy because of carcinoma of the cervix and applied to one ovary 5 to 10 per cent H.E.D., while the other ovary was carefully protected. At operation, which was performed in two weeks, specimens of both ovaries were obtained and studied. The histological picture in the irradiated ovary was comparable to that in the control, no alterations having occurred that could be construed as evidence of degenerative effect.

Wieloch did not obtain any effect in radiation of the sex glands, while Hooker found that in rats the result of gonad radiation was that of stimulation with small doses and sterilization with large doses. Boruttau exposed young animals to x-rays and obtained stimulation as shown by hypertrophy of the graffian follicles, uterus and mammae.

The possibilities of germinal injury through weak irradiation of the ovaries has been exhaustively studied under varying conditions and with conflicting interpretation of results.

One of the most comprehensive papers on this phase of the subject is that of Nurnberger. He recognizes two types of germinal injury: the phenotype, in which there is some anomaly present in the fetus, and the genetic type, in which the immediate product of conception is normally developed but there is a genetic injury which is manifested only in succeeding generations. The time of conception in relation to that of irradiation is of significant importance in the production of germ injuries and permits a division into two groups: 1. Conception was already present in the ovum at the time of irradiation (Fruition in Stadium der Schadigung). 2. Conception takes place at some time subsequent to the irradiation (Fruition in Stadium der Restitution).

Nurnberger was able to collect 200 instances of pregnancy occurring subsequently to ovarian radiation. Of this number, 4 resulted in the birth

of infants with congenital anomalies. Since this proportion is within the normal limits, according to Nurnberger, he considers that the phenotype injury is an improbable result of irradiation of the ovary. He furthermore contends that if an irradiated mother gives birth to a child with congenital anomalies, the probabilities are that she would have given birth to this type of child even if she were not radiated. Nurnberger's figure of above 3 per cent for the normal incidence of congenital anomalies is higher than that accepted by others, as for instance, Plettrichs, who places it at approximately one per cent.

Bagg and Little were able to demonstrate that mice born of irradiated males and females were themselves apparently normal, but succeeding inbred generations displayed congenital anomalies. The results of their experiments are not accepted as conclusive by Nurnberger, who feels that because of the inbreeding the anomalies were probably recessive in nature and not traceable to the original irradiation. There also seemed to be a selective action as the maldevelopment occurred only in the descendants of one pair. He himself observed no anomalies in 114 animals in the second and third generations of irradiated progenitors. He contends that genetic germinal injury is so seldom seen as to make it of negligible practical significance in radiation therapy of women.

Drips and Ford duplicated the experimental studies of Nurnberger and succeeded in obtaining rats of the second and third generations without the occurrence of a single anomaly. They concur with him that pertinent evidence indicating germinal injury has not been substantiated in the range of low dose radiation, i. e., 5 to 10 per cent erythema dose.

Martius, Hofbauer, Holzknecht and Driesen represent a large group who contend that one must keep in mind the danger of both types of germinal injury in every radiation of the ovaries in women during the reproductive period.

Flaskamp has noted a tendency to abortion in the first pregnancy immediately following radiation, but succeeding pregnancies tend to be normal. He did not observe any anomalies in the aborted fetuses.

Holzknecht objects to radiation of the ovaries in young women on the ground of possible injury to the quiescent as well as the mature follicle.

Douay, however, feels that it is not fair to ascribe eventual sterility to this treatment. The application of roentgen rays in young girls with intractable menorrhagia is the last resort in some instances before hysterectomy.

HYPOPHYSIS

Radiation of the hypophysis in small dosage has been advocated in a number of conditions varying in etiology from those in which there is a more or less definite pituitary dysfunction to others in which no such relationship could possibly exist. The most promising field for its application seems to be that of gynecological disorders.

Indications for weak irradiation of this gland are: amenorrhea, especially in women who have failed to obtain relief with ovarian radiation, dysmenorrhea, sterility and in untoward symptoms of the climacteric period. Failure has been noted by Hofbauer in infantilism, in amenorrhea which has lasted more than 3 years, and in menstrual aberration in women above the age of 40 years.

Werner reported that in 13 patients treated by small dose radiation of the hypophysis for amenorrhea, improvement was noted in 7 within a few days or few weeks. He also obtained good results in the treatment in 16 women with dysmenorrhea due to various causes. Successful outcome in amenorrhea and dysmenorrhea by means of weak irradiation of the pituitary was reported by Fraenkel, Hofbauer, Borak, Sahler and others.

Hypophyseal irradiation in conjuction with either ovarian or thyroid radiation has been administered in instances in which pituitary treatment alone was of no avail, or it was felt that because of the symptomatology a dysfunction of the other glands existed. In several cases of associated pituitary obesity and amenorrhea, simultaneous radiation of the pituitary and ovaries was utilized by Recasens in 20 per cent H.E.D. doses with fair results as measured by the disappearance of the mentrual disorder. Seitz, in a similar condition, obtained a cure of the amemorrhea and a subsequent pregnancy which culminated in the birth of a normal infant. Drips and Ford applied radiation in doses of 5 to 10 per cent H.E.D. over the pituitary in addition to that over either the splenic or ovarian regions, in cases of metrorrhagia and menorrhagia, and obtained a temporary regulating effect.

Hallebrand noted a transient relief of epileptic seizures during the course of treatment for amenorrhea by means of 25 to 50 per cent H.E.D. radiation over the hypophyseal region. This result tends to confirm Tucker's observation of some evidence of pituitary dysfunction in 63 out of 200 epileptics and in whom treatment with pituitary extracts seemed to produce improvement.

Hofbauer was the first to attempt massive radiation of the pituitary region, in 1922, for climacteric bleeding and uterine myoma, with apparently good results, but the following year he himself refuted his early claims. Since then negative results have been reported by Hirsch, Werner and Reifferscheid. Hofbauer states that the possibility of cerebral injury with light irradiation is not important, as he has found the brain to be resistant even to massive doses.

The untoward symptoms of both physiological and artificial climacteric, such as headache, mental depression, dizziness, flushes, etc., have been found to be amenable to weak intensities of x-rays. Radiation therapy has been directed at the pituitary, the thyroid and the ovaries.

The menopause syndrome is considered by some to be the result of sympathetic stimulation, due to hyperactivity of the hypophysis and

thyroid in the absence of the antagonistic ovarian hormone (Adler, Munk, Schikkele, Mayer, Borak). Borak advises radiation in doses from 5 to 30 per cent H.E.D. of the thyroid and hypophysis in these conditions. He obtained amelioration of symptoms in 35 instances out of 47 patients treated by this method. According to him, hypophyseal radiation should be instituted prior to that of the thyroid in those instances in which the climacteric syndrome is accompanied by an increase in weight, but it should follow thyroid radiation if the symptom complex is attended by a loss of weight. If improvement is not noted within a few days after the institution of treatment, the radiation should be repeated in 8 days. Occasionally a recurrence of symptoms is noted later.

Porchownik reports his observations on 16 women who were treated for climacteric symptoms, 2 of them being of the artificial type, following intense ovarian radiation. He administered 1/6 to 1/10 H.E.D. over the hypophysis, repeating in 3 to 4 weeks if necessary, i. e., if no improvement was noted within ten days after the treatment was begun. Thyroid radiation in 1/3 erythema dose was then resorted to in the event of a failure after the second series. He states that this method of treatment invariably gave good results, evidenced by a drop in blood pressure in addition to general improvement.

This effect on high blood pressure was also noted by Groedel in both artificial and natural menopause by small dose radiation of the ovaries. Werner reported improvement with small dosage of x-ray over the pituitary and mid-brain regions. Seitz quotes M. Fraenkel to the effect that the latter noted excellent results in two women, 34 and 38 years of age, respectively, who had roentgenological climacteric. Small dosage radiation over both the ovarian and thyroid regions was followed by the return of a regular menstrual cycle and subsequent pregnancy in both women within six months. Seitz states that the results are variable, as he has observed both success and failure with 10 per cent H.E.D. in the same type of a case.

Benjamin agrees with Fraenkel and Leschke's opinion that mild radiation of the thyroid, pituitary and adrenal glands, in addition to the ovaries, will play an important part in so-called "rejuvenation."

In analyzing the radiation treatment of the climacteric, one is left with a feeling of uncertainty and confusion. Some authors administered large or middle size doses to the pituitary or thyroid, others utilized small radiation on these glands, while still others used so-called small doses on the thyroid, pituitary and thyroid. The difference in opinion as to the effects of radiation is never so marked as in the treatment of this particular syndrome.

If the symptom complex of the climacteric is due to hyperactivity of the thyroid and pituitary glands and hypofunction of the ovary, then it is difficult to consider improvement from the viewpoint of stimulation of all the glands involved. It would be more reasonable to expect the treat-

ment to consist of measures tending toward a depression in the activity of the thyroid and hypophysis by massive doses and a stimulation of the ovaries by small doses. It is fallacious to conceive of stimulation in all three glands by small dose radiation. If simultaneous or individual treatment of the hypophysis or thyroid in small dosage brings about an improvement in this supposedly hyperactive syndrome, then small doses in this instance are not stimulative.

In 1922 Stokes advanced a method of small dose radiation of the hypophysis for the amelioration and cure of impaired hearing. The dosage he advised was below 1/50 erythema dose, one well under the stimulative line. According to him, the ultimate result that he hoped for was not that of stimulation, but an equilibration by a restoration of the acid-base balance in cell protoplasm. The best results were obtained by a series of 10 to 20 treatments at short intervals, daily if possible. The method was soon taken up by others, notably McCoy, Jarvis, Richardson, Orloff and Siebenman.

While Stokes states that there can be no doubt of these diminutive doses penetrating the skull and reaching the pituitary gland, other workers in this field are not so ready to attribute the beneficial results noted by them to any action on the gland.

Richardson obtained improvement in 60 per cent of his patients in his series of 600 cases of aural disturbances, regardless of their original etiology. He feels that the therapeutic effects might not depend exclusively upon stimulation of the pituitary or the auditory nerve center, but that possibly the nerve itself and associated non-neural tissue might be subject to the action of the rays. He argues that while it is true that microscopic examination reveals very slight, if any, alteration in nerve and brain tissue following x-ray exposure, still it is possible that radiation will affect nerve structures chemo-electrically.

In McCoy's series of 45 patients suffering from various types of deafness, 30 per cent were greatly improved, 50 per cent somewhat improved, and 20 per cent not improved by small dose pituitary radiation. Among the subjects were 6 of otosclerosis, two of whom were greatly improved by treatment. He considers that the method is still empirical, is not harmful but in many instances is beneficial. He theorizes that there must be an absorption of small cell infiltration in the Eustachian tube, and possibly at the termination of the auditory nerve as well as perhaps stimulation of the auditory nerve. The status of possible pituitary stimulation he is unable to place, but he feels that there may be some basis for it on the ground of alteration in blood pressure attending treatment.

Jarvis came upon this method during the course of treatment radiation of hypertrophy of the lingual tonsil, when it was noted that a difficulty in hearing which had been present for ten years had cleared up. On extending the method to other instances of impaired hearing, he found that improvement ensued especially in those patients whose throat symptoms

were part of a general picture of lymphoid hyperplasia. He concludes that the results are due to the beneficial action of radiation upon lymphoid tissue, and to some extent upon the germicidal effect of the rays.

Tousey found that in pituitary radiation for chronic otitis media, the hearing improved after the aural discharge and pain had ceased. He attributes the improvement to pituitary stimulation.

In attempting to find a biological basis for the x-ray treatment of impaired hearing, Pacini photographed the changes produced in the brain and nerve structures produced by small dose radiation. He considers that the alterations indicate that the rays affect the associated cortical centers and the transmissibility.

An endocrine basis for otosclerosis is advanced by Drury, who found after exhaustive scientific studies that there was a distinct endocrine glandular dysfunction in 50 per cent of his patients. He noted a marked improvement in the ear condition upon the exhibition of the appropriate organotherapy. Although the relationship is not entirely clear, he is of the opinion that the pituitary, thyroid gland and ovary are implicated.

It will be noted from this brief review of the literature on pituitary radiation treatment for impaired hearing that the consensus of opinion, even among those who find this method successful, is contrary to Stokes' contention of pituitary stimulation.

Carlson emphatically denies the possibility of pituitary stimulation in the treatment of impaired hearing. He considers the relationship in general between the endocrine system and upper respiratory disorder, and concludes that such a relationship does not exist. When associated with acromegaly, tinnitus and deafness is generally due to an increased intracranial pressure. Stimulation of any nerve organ by way of the pituitary is not tenable, as this gland does not govern directly nor indirectly the metabolism of the brain or its receptors. He considers it ridiculous to suppose that indiscriminate radiation of the head in the general direction of the pituitary is capable of producing regeneration and restoration of the acid-base equilibrium in the cells of the gland and thus bring about a return of hearing.

Evidence of parathyroid dysfunction as cause of disorders in the tract under discussion is as yet extremely doubtful. The sneezing and irritation of the nasal mucous membrane in dogs ascribed to parathyroid deficiency, he thinks, are due to vascular changes in the mucous membrane secondary to disturbances in the irritability of motor and sensory nerves. The gonads, adrenal and pancreas are eliminated in a consideration of possible etiological factors in the production of diseases of the ear, nose and throat. The only gland, according to Carlson, which calls for a thorough investigation from the point of view of possible relation to the infectious disease of this system, is the thyroid.

Hypophyseal radiation has been utilized in the treatment of dystrophia adiposo-genitalis. Variable results have been obtained in this condition

when associated with amenorrhea or other gynecological disorders. Treatment in children by small dose radiation has also met with inconstant results.

Ascoli and Fagiuoli obtained remarkable improvement in a case of Froelich's syndrome associated with asthma in a boy 15 years of age. Pituitary radiation was tried after he had been on pituitary extract and other organotherapy for a long period of time. The treatment consisted of weak irradiations one month apart for four months. Twenty-five days after the initial visit there was an increased activity in both primary and secondary sex characteristics as evidenced by an increase in pubic hair, increase in the size of the penis, increase in height, decrease in fat, appearance of erections, which became more frequent and complete, and the accentuation of sexual appetite.

Similar results are reported by Wieser of Vienna in several instances of this disease. Carlson considers these cures as modern miracles, and states that "Evidently we are witnessing the beginning of a race between the roentgenologists and surgeons as harbingers of virilism."

Ascoli and Fagiuoli were unsuccessful in the treatment of eunochoidism in a man of 26 years of age in whom they radiated by small doses the pituitary, thymus and testes.

Wintz feels that hypopituitarism even in its extreme degree, as exemplified in Simmons' disease, is not to be treated by weak irradiation of the gland.

Detailed reference will not be made to the numerous experiments which have been performed in the laboratory on the effects of weak hypophyseal irradiation.

Suffice it to say that the results are not conclusive, some obtaining an increase in growth, while others noted a diminution in addition to the production of genital hypoplasia. To complicate the subject still further, Poos claims that whenever any organ is exposed to the action of the x-rays, a pathological change takes place in all radio-sensitive organs. He obtained the same result on raying the legs of animals as on radiating the hypophysis.

In any consideration of the effects of radiation of the pituitary, one must take cognizance of the anatomical and functional relationship existing in this region of the mid-brain. Here are controlled metabolic processes, water exchange, heat regulation, sexual development and certain endocrine functions. Localized radiation must necessarily act on both the hypophysis itself and on the vegetative centers in its vicinity; how much of the functional activity attributed to the gland is performed by the surrounding structures is still a mooted point.

ADRENAL

In any evaluation of the effects of irradiation on the adrenal, consideration must be given to the variable radio-sensitivity of this gland

According to Holfelder and Peiper, this varies to such an extent that it is exceedingly difficult to state in advance the effect of any given dose, thereby explaining the contradictory results obtained with the same dose in different individuals. The adrenals are twice as sensitive as the intestinal epithelium and should therefore be excluded from the field of exposure in the treatment of other organs in their vicinity.

These limitations upon adrenal radiation therapy must be kept in mind in evaluating the reports in the literature.

David and Hirsch studied the action of radiation upon the adrenalin and blood sugar content in guinea pigs, dogs and rabbits, one adrenal being exposed while the other was protected. They found that distinct functional increase resulted from a 25 per cent H.E.D., as evidenced by an increase both in the blood sugar level and adrenalin content. Larger doses, one H.E.D., produced a distinct diminution in function. Their observations have been confirmed by Hesse.

Golobinin reports his findings in a case of Addison's disease in a man 27 years of age. Long continued organotherapy was without effect, but after small dose irradiation of the adrenal region improvement set in, as evidenced by an amelioration of the general condition, increase in weight and disappearance of the cutaneous pigmentation. The treatment consisted of small doses (strength not stated) for 50 sittings over a period of 70 days. Wiesner also obtained improvement with a similar method of long continued treatment.

Holfelder and Peiper protest against what they term these blind methods of treatment without first knowing or determining the radio-sensitivity of the adrenal glands of that particular patient. There are several reports of injury to the adrenals following radiation, such as that of Harvey, who found evidences of bleeding in the adrenals and degenerative changes in the zona glomerulosa. Descastellos and Zimmern and Cottenot observed adrenal injury, the latter, however, after larger doses (3 to 6 H.E.D.).

Levy-Dorn and Weinstein obtained a transient slight rise in blood pressure following small dosage, but they were unable to determine any definite relationship between the intensity of the reaction and the strength of the dose. Results such as these are not accepted by other investigators, as, for instance, Holfelder and Peiper, who conclude on an experimental basis that the possibility of diminishing functional activity of the adrenal cortex by irradiation is plausible, but the medulla does not seem to be influenced by x-rays. The reduction of adrenal function in terms of blood pressure is at least problematical. The idea of a stimulating dose must remain for some time a Utopian one.

There are numerous reports in the literature on the effect of irradiation of the adrenals in so-called small doses in diabetes mellitus (Stephan, Dresel, Zimmern, Cottenot and Beumer). On study of the reports, it is found that the exact strength of the dose is not mentioned or else it was

above a 25 per cent erythema dose, and therefore cannot be accepted as being an instance of small dose radiation. Practically all of the reports show a diminution in glycemia and an improvement in diabetes mellitus, surely not an example of stimulation, if it be conceded that the adrenal gland is hyperactive functionally in this disease. These results should be construed as tending to show that radiation of the adrenals in doses larger than 25 per cent H.E.D. may produce temporary recession of diabetes mellitus by a diminution in adrenal activity.

THYROID

In contradistinction to the vast amount of literature on the x-ray treatment of exophthalmic goitre and hyperthyroidism, there is a paucity of information on the effects of weak irradiation of the gland in hypothyroidism, in spite of the fairly frequent occurrence of the latter condition.

Stimulation of metabolism as evidenced by an increased basal rate and hyper-excitability of both motor and sensory nerves has been observed by Leo Loeb. Increased functional activity in reference to carbohydrate metabolism has been noted by Broslamen, who found a hyperglycemic curve following small dose radiation and a depressed curve after large amounts of radiation.

McCord and Marinus report some interesting experiments in which they studied the rate of metamorphosis in normal tadpoles, in non-irradiated but thyroid-fed tadpoles, in irradiated only and in those which were irradiated and then subsequently fed thyroid extract. It was noted that irradiation itself is without any apparent effect on normal tadpoles, but that it increases the functional activity of thyroid extract when administered subsequently by an alteration of the susceptibility toward that hormone. This change in the cellular susceptibility or in the production of a subsequent increased hormonic activity was also demonstrated by Fogelberg, who studied the effects of radiation in small doses on the sugar curve in 22 patients; 2 of these were normal, 4 had simple goitre, 3 exophthalmic goitre and 13 thyrotoxicosis. All failed to show any effects after simple, weak thyroid irradiation, but on the subsequent ingestion of 100 grams of glucose presented a typical hyperglycemic curve.

The relationship of certain skin conditions to thyroid hypofunctioning has been stressed lately, especially in eczema and scleroderma. Guarini and Donah report improvement in eczema following the administration of weak irradiation of the thyroid.

Ascoli and Fagiuoli noted improvement in scleroderma in a woman 56 years of age after irradiation of both the thyroid and pituitary regions. Hammer accepts the basis of a dysfunction of the thyroid in this condition, but claims that the x-rays decrease the functional activity of the gland instead of increasing it. In his two patients, one of whom had a thyrotoxicosis and the other a simple goitre, weak irradiation of the thyroid resulted in a clearing up of the scleroderma.

Thyroid radiation has been utilized in both massive and weak intensities in the treatment of gynecological conditions, but in order to place roentgenotherapy of this gland upon a rational basis in this field, it must first be determined whether one is dealing with an increased or a decreased functional activity of the gland.

According to Wintz, thyroid-ovarian disorders may be grouped under the following classification: (1) Thyrogenous dysfunction of ovary secondary to a hyperthyroidism. (2) Oophorogenous hyperthyroidism, the primary ovarian condition being exemplified in operative removal of the ovary and in disappearance of ovarian function in both physiological and artificial menopause. (3) Ovarian dysfunction upon the basis of hypothyroidism. In this condition, amenorrhea is accompanied by dry skin, edema, water retention and obstipation.

In the treatment of any of these disorders, the underlying cause must be eradicated before a cure can be expected; any other measures are merely palliative. Weak irradiations are, of course, contraindicated in hyperthyroidism of both primary and secondary types. In the third type, that of simultaneous ovarian and thyroid dysfunction, the results of weak irradiation directed against the thyroid are apparently not as effective as against the ovaries. Wintz and others advise that in these conditions irradiation of the ovaries be accompanied by the administration of glandular material. Sehrt, Seitz, Wintz, Recasens and others have obtained good results in hypothyroid amenorrhea with the use of ovarian and thyroid extracts, but they have noted a recurrence of the amenorrhea attending the discontinuation of thyroid extract.

Wieser reports the results of radiation of 360 patients with various endocrine disorders. As it was not always possible to arrive at a diagnosis upon the basis of the history and clinical findings, he utilized the Abderhalden test and the exchange of gases in addition. Upon the basis of these methods of diagnosis, he radiated the pituitary, thyroid and gonad, administering 2 to 10 per cent H.E.D. over the gland or glands involved every four weeks for about three months. In some instances a second series was necessary, and in others a transient retrogression was observed in about three weeks after the onset of treatment. Organotherapy and other treatment directed against the original etiological factor, such as lues or tuberculosis, was simultaneously given. Only 4 per cent failed to give some response. He includes mongolian idiocy among the conditions which were not amenable to treatment, but he further reports marvelous improvement in two children with this otherwise intractable disease. These patients were 3 and 7 years of age, and after radiation the characteristic earmarks of this condition, such as over-extension of the joints, epicanthus and cutaneous manifestations, were altered to so marked a degree that it was barely possible to recognize the children as mongolian idiots. Other instances of astounding results were obtained in imbecility, dwarfism, dysgenitalism,

chondrondystrophy, homosexuality, behavior disorder, Froelich syndrome and myxedematous idiocy.

PARATHYROID

There are no available clinical reports of parathyroid radiation, due to the difficulty in radiating this gland without at the same time affecting the thyroid. Experimental reports of increased calcium content after weak dosage of x-rays directed at this gland must be considered from the same viewpoint.

THYMUS

The meager literature on the effects of weak irradiation of the thymus is concerned for the most part with their results noted in the treatment of skin disorders. We find here the same controversial discussion as to the causal relationship of the gland, some, like Brock, Weinhardt and Klingmuller, contending that there is such a connection, while others, like Schneider and Weber, disputing the claim.

Brock has observed improvement with weak irradiation in lichen planus, psoriasis, ichthyosis and varrucosis. Weinhardt and Parker also obtained good results in psoriasis, the latter asserting that a cure can be obtained in 85 per cent of the cases by means of this treatment. Steiger assumes that the thymic dysfunction belief is substantiated by the observation that children with status thymo-lymphaticus rarely have psoriasis.

Schneider has not been able to obtain the results reported by Brock, as he succeeded in only two cases out of 12 in clearing up the condition. Instead of an improvement, Weber observed an aggravation of psoriasis in his patient.

Thymus radiation has been used in exophthalmic goitre. Ascoli and Fagiuoli noted a recession of the goitre and an improvement in hyperthyroid symptoms in two patients subjected to thymic radiation in small dose.

Most exacting experiments were carried out by Lenz, who studied the alterations produced in the thymus glands of rabbits by varying strengths of radiation. The gauge of stimulation was the increase in the number of mitotic figures as shown by Dustinn in his experiments in mice after intraperitoneal injection of horse serum. Lenz's results may briefly be summed up as follows: A single large dose produces involution of the thymic parenchyma with complete absence of mitotic figures. With moderate doses, regeneration takes place in 11 to 12 days, as shown by the appearance of mitotic figures, and is complete in approximately three weeks. With small doses there is a progressive involution of the parenchyma, but no demonstrable attempt at regeneration. The experiments show that thymic glands which are the seat of either age or accidental involution cannot be stimulated by even as small a dose as 1/40 erythema dose, but on the contrary, normal involution progresses more rapidly. Lenz claims that this rapid destruction of the thymus probably upsets the endocrine balance

of the body and liberates proteins previously kept in combination with the parenchymal cells. Whether clinical improvement occasionally seen after irradiation of the thymus can be explained on this basis or not, stimulation of this organ is not responsible for the change.

Manfred Fraenkel has recently advanced the opinion that certain glands possess the power to combat cancerous growth, and that stimulation of these glands will result in checking its progress. He has advised weak irradiation of the thymus and thyroid in mediastinal tumors and of the pituitary in carcinoma of the eye. This conception is of too recent a date to be discussed here.

The thymus is considered to be involved in epilepsy from the view point of both an increased and diminished functional activity. Strauss believes the condition to be due to endocrine dysfunction and advises radiation in small doses of the adrenals and thymus. Symmers, on the other hand, has noted that epileptic seizures often cease at puberty, at the time when the thymus gland undergoes involution with a resultant diminution in gland activity. On this basis, he advises intense radiation of the thymus in those epileptics especially who show stigmata of status thymolymphaticus.

PANCREAS

The results obtained in weak irradiation of the pancreas are not sufficiently definite to warrant the expression of any opinion at the present time.

Peterson and Saelhof conclude from their experiments on dogs that in pancreatic deficiency due to partial pancreatectomy, roentgen irradiation of the pancreatic rest produces a transient increase in sugar output, which is followed by an increase in carbohydrate tolerance. The increased tolerance may be transient or may extend over a period of several weeks. The effect on the blood sugar varies; there is usually a temporary increase, to be followed by a lowering of the level within a few hours to several days. The effects are attributed by the authors to direct stimulation of cellular metabolic processes and not to vascular alterations. They feel that the changes in carbohydrate metabolism accompanying various strengths of radiation over the pancreas are in keeping with the Arndt Schulz phenomenon. It is felt that the clinical application of weak irradiation in the management of diabetes mellitus is not to be considered, however, until further knowledge concerning the ultimate effect of x-ray stimulation on pancreatic tissue is obtained. The authors feel that its use in diabetic coma may be warranted when other types of treatment have failed.

Stephen exposed the pancreatic region to stimulating doses of x-rays, and observed in two cases of diabetes mellitus an increased tolerance for carbohydrates and a diminished excretion of sugar.

In evaluating the effects of pancreatic irradiation, it must be remembered that an augmentation in the sugar output may be due to general radiation and stimulation of the abdominal viscera by secondary rays.

TESTES

There is very little available literature on the effect of weak irradiation on the testes. Wolf claims that they are more radio-resistant than other glands and require from 3 to 5 times as large a dose as the ovaries to obtain approximately the same results.

Benjamin reports the administration of roentgen rays on the testes in supposed hypofunction, but he was unable to obtain any result tending to show any increase in gonad function.

CONCLUSION

In this paper there has been presented a review of the literature on the so-called stimulative effects of roentgen rays on endocrine glands.

The question at issue is not the presence of an increase in body weight, activity and functional capacity following irradiation in small doses of x-rays, but the determination as to the fundamental underlying cause of this reaction—is it a direct stimulative effect or is it the result of complicated processes not stimulative in nature?

From a clinical view point, weak irradiation does increase functional activity as especially illustrated in the treatment of gynecological disorders by irradiation of the ovaries. The clinical application of pituitary radiation, while beneficial, does not imply always a stimulating action; some of the results are probably due to destructive effects. The results noted in the treatment of childhood endocrinopathies by irradiation of the thyroid, pituitary and gonads are startling at the hands of one particular investigator, but they should be confirmed by others before they can be accepted. Radiation of the adrenals, pancreas, testes and parathyroid has not given us any definite information as yet in the treatment of dysfunction of these glands.

Stimulation by means of roentgen rays may in time be one of the methods of procedure in the treatment of endocrinopathies, but before this is possible it must be placed upon a scientific, accurate and rational basis. A proper knowledge of the underlying endocrine factors in the causation of the disease and a standardized method of radiation with a standardized table of dosage are necessary requisites before any hope can be entertained for success in stimulative radiation.

SUMMARY

This paper is a review of the literature on the stimulative effects of x-rays on endocrine glands. A biological basis for the stimulative action is found in the Arndt Schulz law, which states that "weak stimuli accelerate vital processes, moderate promote them, strong inhibit them, and strongest destroy them." The increased functional activity noted after radiation is interpreted according to two view points: Fraenkel believes that there is a direct stimulative effect on the cells in accordance with the Arndt Schulz law, while Holzknecht and his school deny any stimulative

action, claiming that x-rays always destroy in no matter what dosage. They contend that increased cellular activity is due to the freeing of a restraining influence of a depressing factor.

Thousands of experiments have been performed on seeds, vegetations, plants and micro-organisms demonstrating that this law is valid and is applicable to the action of x-rays. This is denied by others, who in addition feel that the entire concept of growth promotion in plants and in cellular organisms is not equivalent to that of the complex mechanism obtaining in the human body.

It is difficult to evaluate or compare results in the reported cases because of lack of uniformity in expression of dosage and in standardization of strength. The small dose of one author is a moderate strength of another.

The widest application of small dosage radiation has been in the field of gynecology. There is enough clinical evidence showing favorable results from weak irradiation of the ovary to justify its use in carefully selected cases. Successful outcome has been reported by many authors in more than 50 per cent of their cases of amenorrhea, as evidenced by the return of a normal, regular menstrual cycle and in the occurrence of more than 200 instances of a subsequent pregnancy, with the delivery of a normal infant in all but 2 per cent. While some minimize the dangers, the possibility of germinal injury must be thought of in the ovarian radiation of any woman during the reproductive period. The results in the treatment of dysmenorrhea and oligomenorrhea have been fair. Some authors claim that the ultimate outcome of radiation therapy in gynecological conditions depends upon the age of the patient, the duration of the disorder and the thickness of the abdominal walls.

Untoward symptoms of both physiological and artificial climacteric periods have been treated by irradiation of the pituitary, thyroid and ovaries with amelioration in most instances. Some administered large or middle sized doses to the pituitary or thyroid, others utilized small radiation of these glands, while still others used so-called small doses on all three glands. If the symptom complex is due to hyperactivity of the thyroid and pituitary glands with a hypoactivity of the ovary, then it is difficult to consider improvement from the viewpoint of stimulation of all the glands involved. It is fallacious to conceive of stimulation in all three glands by small dose radiation. If simultaneous or individual treatment of hypophysis or thyroid in weak intensities brings about an improvement in this supposedly hyperactive syndrome, then small doses in this instance are not stimulative.

Pituitary therapy in impaired hearing, as advocated by Stokes, has no scientific basis, and the results are not considered as being due to stimulation of this gland even by the majority of those who have obtained good results following its use.

Treatment of Froelich syndrome has not been uniformly successful with weak irradiations, especially when accompanied by amenorrhea.

The radio-sensitivity of the adrenals is so marked that it is difficult to state in advance what the result will be with any given dose. The effects of weak irradiation of this gland have not been uniform for this reason; some of them have been increase in blood pressure and in the blood sugar level. A few instances of improvement in Addison's disease have been reported.

There is a paucity of information on the utilization of weak radiation of the thyroid in hypothyroid states, in spite of the fairly frequent occurrence of the condition. Increased functional activity, as evidenced by an increase in basal metabolism and sugar metabolism, have been noted in the laboratory. Improvement in eczema and scleroderma and in ovarian dysfunction due to hypothyroidism, has been reported, but in the latter condition benefits are noted only during the time of simultaneous oral administration of thyroid extract.

Startling results are reported by Wieser of Vienna in the treatment of childhood endocrinopathies and related conditions, including mongolian idiocy, by irradiation of the pituitary, thyroid and gonads. Where the diagnosis cannot be made upon the history and clinical picture, the Abderhalden test and gas exchange are utilized.

There are no available reports on the effect of radiation of the parathyroid. It would be difficult to radiate this gland without at the same time striking the thyroid.

Exacting experiments by Lenz force him to the conclusion that there is no evidence of any stimulative effect on the thymus as the result of weak irradiation.

M. Fraenkel has recently advanced the opinion that certain endocrine glands possess anti-cancer influence, and upon this basis advises stimulative irradiation of the thymus and thyroid. This concept is of too recent date to be discussed here.

Improvement has been noted by several in the irradiation of the thymus in certain skin conditions.

There are a number of case reports in the literature on the beneficial effect of small dose radiation in diabetes mellitus, but on analyzing the original papers, it is found that either the exact doses are not mentioned or else a strength above 25 per cent H.E.D. was used—surely not an example of a small dose. The results obtained by small dosage radiation of the pancreas are not sufficiently definite to warrant the expression of any opinion at the present time. Increased carbohydrate tolerance has been reported after weak irradiation, but it is felt that the clinical application of this method of treatment should not be considered in the management of diabetes mellitus until there is further light on this subject.

There is very little available literature on the testes or pineal.

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THE USE OF CORTIN IN ADDISON'S DISEASE

FRANK A. HARTMAN, A. H. AARON AND J. E. CULP*

From the Physiology Laboratory of the University of Buffalo and the Buffalo General Hospital

BUFFALO

Cases of Addison's disease have been treated by adrenal preparations (Rowntree, 1; Cohoe, 2). Whole gland or whole cortex have been used. Some cases showed definite improvement.

Cortin, a substance obtained from the adrenal cortex, enables adrenalectomized cats and rats to survive indefinitely (3), (4). If Addison's disease is due to a deficiency of cortin, the injection of the latter should ameliorate the condition.

We are reporting the effects of cortin injections in one case. This is warranted because repeated reduction or withdrawal of the substance has demonstrated conclusively that the patient is kept alive by cortin. Not only was the patient revived from an apparently moribund condition but four times the cortin has been reduced or discontinued and each time there has been a decided relapse. Recovery from these relapses occurred when cortin was increased.

The patient, a man 24 years old, had scarlet fever in February, 1928, the illness lasting one month. During the winter of 1929-30 he continued to work but did not feel like going out in the evening as he had previously. He remembered two attacks of gastric upset in this period.

At the time of admission to the hospital he had been very ill for six weeks. Nausea and frequent vomiting made it difficult to retain any but liquid foods. His weight had been reduced about twenty per cent. He showed characteristic pigmentation. The face, neck and forearms, parts which had been exposed to the sun (he had worked outside), appeared to be strongly sun-burned, but in addition there were small "black freckles" plentifully distributed over the body in protected as well as unprotected regions. There was a brown streak on the skin above the spine and brown discoloration on the hips apparently where clothing had pressed against the body. There was also brownish pigmentation of the gums over the two central upper incisors.

When first seen he appeared to be in shock. His pulse was feeble. His blood pressure was 50 mm. systolic, 20 mm. diastolic in both arms. He complained of feeling cold. Blankets and hot water bottles were applied. Every available method was adopted to introduce water into the tissues. At first 1000 cc. of isotonic NaCl solution was introduced by hypodermoclysis. Small amounts of fluid were taken by mouth. Six hours later 1000 cc. of 5 per cent glucose in isotonic NaCl solution were

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injected intravenously and glucose was given by the Murphy drip method. Between four and five liters of fluid was introduced into the tissues during the first twenty-four hours. He was quite drowsy and dozed much of the time. At the end of the 24 hours he was no better; his blood pressure was 58/30. His pulse was very weak and thready. He was extremely restless so that he kept moving his legs, hands and feet. His legs twitched and he complained that they felt numb and tingled. He talked irrationally.

Adrenalin (1 cc.) was injected subcutaneously every two hours but was discontinued by the third day. One liter of 5 per cent glucose in isotonic NaCl solution was given intravenously twice every 24 hours for seven days. Digitalis was given for three days.

Cortical extract was not available until 24 hours after admission. An injection of 5 cc. was then made intravenously. Thirty minutes later 10 cc. was given subcutaneously. Three and one-half hours after the first injection three injections (10 cc. each) were made subcutaneously with forty and seventy minute intervals. Additional extract was not available for four hours, but after that 10 cc. was injected subcutaneously every hour until a total of 150 cc. had been injected in the twenty-four hours. The amounts injected after this are indicated in the chart (1 cc. contained the yield from about 15 gm. of cortex).

Three hours after starting the cortical extract the patient was quieter. At nine hours the pulse was 100 per minute, the temperature 100 and the respiration 26 per minute. He again became irrational and voided urine in bed a number of times. By morning (20 hours after cortical extract was instituted) he was sleeping at long intervals but was very restless when awake. During the next night he was very irritable and hard to manage. His pulse was of fair quality and his blood pressure was 74/32. He improved during the third day, dozing much of the time. He slept most of the third night and seemed much brighter in the morning. He ate his first meal (breakfast) at this time. He read and took an interest in his surroundings. His appetite and general condition continued to improve so that by the fifth day after instituting cortical extract he was eating bread, butter, chicken and potato. He no longer slept much in the daytime, his night's sleep apparently being sufficient. He appeared fresh and rested when observed in the morning. His mental activity also increased. He read much of the time and talked with visitors.

It will be noted in the chart that the amount of cortical extract was gradually reduced until he was receiving only 20 cc. in 24 hours (5 cc. every six hours). Eleven days after cortical extract had been started he refused food at noon and complained of feeling cold that night. The next morning orange juice nauseated him and by eleven A. M. he was very ill. Cortical extract (10 cc.) was given intravenously and two more injections (10 cc. each) within an hour. Extract (10 cc.) was then given subcutaneously every hour for thirty-six hours and then every two hours for a few days as the chart indicates. With this relapse temperature rose, blood

pressure fell, pulse rate increased and the old symptoms returned. He became cold, restless and mentally dull. He slept much but did not appear rested. He was easily nauseated. Fluids were administered as before and glucose injected twice daily for three days. Within two days after increasing the extract the patient showed marked improvement. Blood pressure had risen; the pulse was slow and of fair quality. There was mental alertness instead of restlessness and apathy. Nausea was absent and the patient began to eat. He steadily improved.

In an attempt to find the minimum dosage required, the extract was reduced on the twenty-fifth and thirty-fifth days. A few days after the second reduction the old symptoms appeared, viz., loss of appetite, nausea, vomiting and asthenia. An increase in dosage brought about recovery.

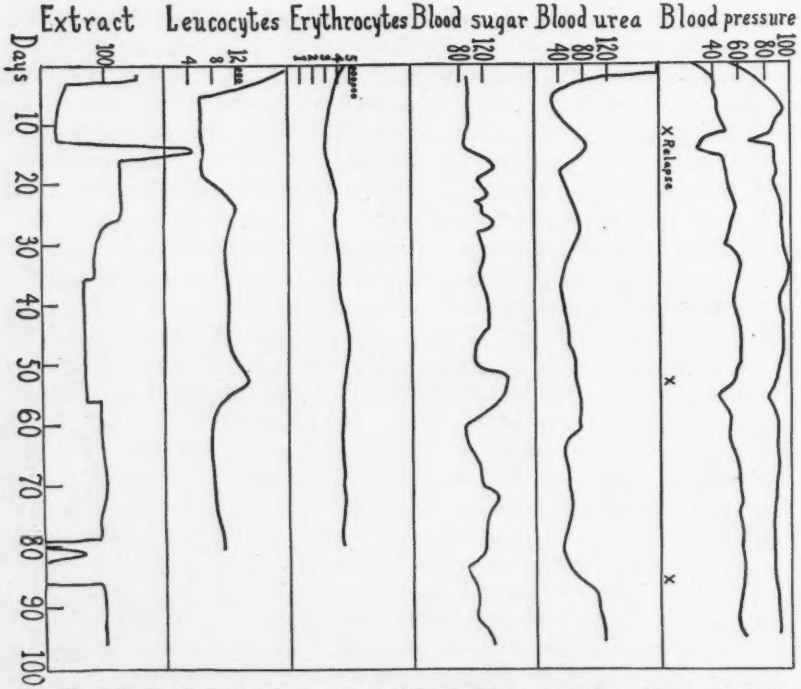

Chart I. Blood changes in a case of Addison's disease beginning with an attack that threatened to be fatal. Injection of cortical extract produced recovery. Reduction of extract caused serious relapses(x). Blood urea and blood sugar in mgm. per 100 cc. Extract in cc. (Blood urea should be 130—120 at first.)

The extract was discontinued except for one day for about eight days beginning on the seventy-eighth day. In about three days after discontinuance the old symptoms reappeared. Injections caused them to disappear.

It is difficult to account for these effects except through the action of cortin.

Certain changes have been observed which will be discussed.

Temperature: The patient has had fever twice; first, for five days after entering the hospital, and second, during the first relapse. At all other times the temperature has been subnormal. During the second relapse the temperature ranged about 97° F. This lasted about two weeks. At other times it ranged about 98° F.

Pulse: The pulse rate has ranged from 70 to 90 per minute except during the febrile periods.

Blood Pressure: The highest the systolic pressure has been is 100 mm. Both systolic and diastolic pressures have fallen during the relapses, although only to a small extent during the third one (see chart).

Blood Urea: The blood urea was very high (130-120 mgm. per 100 cc.) during the first three days after admission, but as the symptoms disappeared it fell rapidly. It gradually rose again as the extract was decreased and again fell with the second remission.

The blood urea has risen with each relapse, but does not keep pace with the condition of the patient. He may be very ill before the urea shows much of a rise. There may also be a lag upon recovery. The urea does not necessarily fall promptly with amelioration of the symptoms.

It has been found in adrenalectomized cats (5) that the blood urea becomes very high in the terminal stages. If the animal recovers the blood urea falls. It has also been shown in animals that a high blood urea can be reduced by the injection of cortin.

Rowntree (1) has shown that the blood urea falls when the patient improves.

Blood Sugar: The blood sugar was low (82-86 mgm. per 100 cc.) even during the administration of glucose. It remained low until after the first relapse. It has fluctuated considerably as shown by the chart.

Blood Cells: Changes in the number of erythrocytes and leucocytes are shown in the chart. The large count at the beginning is probably accounted for by dehydration. The highest erythrocyte count was obtained 42 days after beginning treatment.

Following each relapse during recovery there has been extensive desquamation of the skin.

Addendum: A fourth relapse occurred after the chart was made. Increase of extract produced recovery. It has now been more than five months since treatment was started.

The results in this case indicate that cortin deficiency is an important factor in the causation of Addison's disease.

SUMMARY

A subject of Addison's disease with notably dubious prognosis was revived and has been kept alive for more than five months by the injection of extract of the adrenal cortex. Four relapses have occurred following reduction of the extract. A few hours after increasing the extract after a relapse, improvement was evident each time, and in two or three days

recovery was almost complete. The appetite returned and mental activity became normal.

Each relapse was accompanied by a fall in blood pressure and a rise in blood urea. Blood sugar was low during or after a relapse.

We wish to thank Drs. L. M. Lockie and G. W. Thorn for their help in this study.

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Abstract Department

Neural and hormonal influences on bodily activity. Differential factors controlling the heart rate during emotional excitement. Britton, S. W., A. Hinson and W. H. Hall. Am. J. Physiol. **93**: 473. 1930.

Evidence indicating that growing importance which is related to the frequency of the heart beat and its connection with cardiac output and metabolism is briefly discussed. Experimental analysis is made of the various factors involved in regulation of the heart rate in the cat during an intense emotional reaction attended by moderate muscular activity. Quick reflex changes in rate, i. e., those occurring within a minute or so after excitation, are mediated only through vagal, thoracic, sympathetic and adrenomedullary influences. Any one of these three influences may be eliminated without significant effect on the normal cardiac increments occurring during excitement. The removal of any two factors normally concerned in regulating the activity of the heart is shown markedly to reduce its acceleratory ability—usually by about 50%—following vigorous excitation of the unanesthetized animal. This incapacity persists throughout repeated stimulation extending over many weeks. If all three cardio-regulatory factors are eliminated only negligible variations in rate occur during excitement. In over 100 cases in which normal animals were excited for one and a half minutes the average increase in heart rate was approximately 50% over the basal level. Animals which were subjected to emotional stimulation every second day throughout an eight-weeks' period showed no diminution in cardiac response, and thus exhibited no tolerance towards the excitation.—Authors' Summary.

Seasonal variations in survival of adrenalectomized animals. Britton, S. W., Am. J. Physiol. **93**: 637. 1930.

The effects of adrenalectomy were studied in the marmot (Arctomys monax). In the summer these animals rapidly succumb—usually within ten days—following removal of both adrenal glands. Indefinitely long periods of survival are, however, observed—extending at least over a few months—in animals operated on during the winter. The marmot is very active in summer, and its blood sugar at this time is high and normally between 120-190 mgm. per 100 cc. During the colder weather, although hibernation does not usually occur in captivity, these animals show much less activity and their blood sugar is much reduced—particularly so in the case of adrenalectomized animals. The body temperature also reaches lower levels. The greatly protracted survival periods observed in winter in marmots deprived of adrenal tissues are possibly referable to reduced metabolic activities.—Author's Abst.

Seasonal variations in survival after adrenalectomy. Britton, S. W., Am. J. Physiol. **94**: 686. 1930.

The marmot (Arctomys monax) survives adrenalectomy for 2 to 10 days only when operated on between April and November, or during the normal active period for this hibernating type. Animals which are adrenalectomized during the winter months, when normally inactive or dormant, suffer no immediate ill effects from the operation, and may survive in good health for several months. At the usual time of awakening to activity in April such animals show severe signs of adrenal insufficiency and quickly succumb. The blood sugar, body temperature and heart rate of the marmot were found to be considerably lower during the normal period of dormancy than in summer. There is also a much diminished energy output during hibernation. The intimate relationship of the adrenal glands to metabolism is briefly discussed.
—Author's Summary.

Some observations on adrenaline action on the pulse (Alcune osservazioni intorno all' azione dell' adrenalina sul polso). Canziani, G., Riv. di pat. nerv. **35**: 183. 1930.

Adrenaline effects upon the blood pressure can be employed for diagnostic purposes because of their relative constancy. The pulse rate should not be used, because of its irregular and inconstant response.—G. Coronedi.

The mechanism of epinephrine action. VII. Changes in the glycogen, lactic acid and phosphate content of muscle. Cori, Gerty T., Am. J. Physiol. **94:** 557. 1930.

The glycogen content of the right and left gastrocnemius muscle, when extirpated at 30 minute intervals from rats under amytal anesthesia, was found to be of the same magnitude. When after extirpation of the first muscle epinephrine was injected either subcutaneously or by means of an intravenous infusion at a constant rate, a definite reduction in the glycogen content of the second muscle was always encountered. Twenty and 40 minutes after epinephrine injection the phospho-creatine content of muscle was practically unchanged, the inorganic phosphates showed a slight decrease and the lactic acid content of muscle and of blood was markedly elevated.

—Author's Summary.

Addison's disease associated with congenital absence of suprarenal glands. Crosby, E. H., Arch. Path. **10:** 38. 1930. Abst., J. A. M. A. **95:** 754.

The case of a woman who died at the age of 35 years is reported. At necropsy no gross evidence of suprarenal tissue could be discovered. Microscopically, small islands of suprarenal cortex were found near the superior poles of the kidneys embedded in retroperitoneal fat. It is evident that in cases such as this the embryonic development of the suprarenal gland has been faulty, but that cortical and medullary tissue has existed in sufficient amount to sustain life for many years, finally to become exhausted, a condition resulting in typical Addison's disease and death.

The mechanism of adrenalin glycemia. Dworkin, S., Am. J. Physiol. **93:** 646. 1930.

Recent work (Cori and Cori) on the function of adrenalin in carbohydrate metabolism indicates that the adrenalin hyperglycemia is due to some inhibitory action on peripheral sugar utilization, rather than to conversion and release of stored glycogen. These conclusions have been adduced from experiments with rather large amounts of adrenalin, administered subcutaneously and assumed to be absorbed at a slow rate. We have studied the effects of much smaller quantities of adrenalin—0.001 to 0.004 mgm. per kgm.—injected intravenously, in single doses. Most of the experiments were carried out in cats under amytal anesthesia; a few in normal cats, and in dogs. Provided that the blood sugar level to start with was below 130 mgm.%, there was rarely found, with the amounts of adrenalin used, an increase in blood sugar beyond the renal threshold, or above 70 mgm. per 100 cc. In many experiments the denervated heart was used as an indication of the presence of adrenalin in the blood stream. When, under these conditions, small amounts of adrenalin were injected intravenously (or liberated by splanchnic stimulation) the duration of the increase in the heart rate never exceeded 10 minutes; often the peak was reached in less than 3 minutes; and the glycemia sometimes outlasted the heart rate increase by 40 minutes to 3 hours. If adrenalin, as such, produced the glycemia, it must have exerted its action in a few minutes—a view hardly compatible with the idea that adrenalin raises blood sugar by decreasing sugar utilization. There is, of course, the possibility that the adrenalin, quickly removed from the circulation, remained for a long time in the peripheral tissues; proof of this has not been furnished. In any case, it is obvious that the effects from small, intravenous doses of adrenalin are different from those obtained with the amounts referred to above. The fact that splanchnic stimulations give results similar to those obtained with the small amounts indicates that such quantities more nearly correspond to the physiological activity of the adrenal glands.—Author's Abst.

A further study of the hormone of the adrenal cortex. Hartman, F. A. and K. A. Brownell, Am. J. Physiol. **93:** 655. 1930.

The potency of the extracts used by the authors has been tested by their ability to prolong the lives of completely adrenalectomized cats. As controls 8 cats have been injected every 4 hours with a small quantity of 0.9% NaCl solution and 7 cats twice daily with 6 cc. of the same solution. These cats lived an average of 6.2 days, ranging from 1.5 to 10.3 days. In addition 20 animals were adrenalectomized but not injected. They lived an average of 11.5 days, ranging from 2 to 35 days. The average of 35 control cats was

9.2 days. The following tentative conclusions have been reached in regard to the cortical hormone. Keeping the whole adrenal on ice or at about 35° C. for 18 hours before extraction seems to destroy the hormone or produce a deleterious substance which offsets its value. Preserving the gland on ice in the absence of oxygen is more satisfactory. Acetone, apparently, does not precipitate the hormone. The hormone seems to be destroyed by heating to 80° C. for 5 minutes and by dilute alkali. The activity is preserved better by separating the cortex from the medulla and by preservation at a low temperature, if the tissue is to be kept some time before extraction.
—Authors' Abst.

The effect of extracts of suprarenal cortex on the blood calcium. Mirvish, L. and L. P. Bosman, Brit. J. Exper. Biol. **6**: 350. 1929. Abst., Physiol. Absts. **15**: 314.

Injection of alcoholic extract from bovine suprarenal cortex lowers the blood calcium content of rabbits by about 30%. A parallel is drawn between this and the calcium-reducing effect of ovarian secretion. Though no physicochemical tests have been made, it is suggested that this suprarenal hormone is identical with the calcium-reducing hormone of ovary and corpus luteum. It is claimed that this investgation "established a definite relationship between the ovary and the suprarenal cortex."

On adrenal virilism (Sur virilismo sessuale). Ricci, E., Policlinico (sez. prat.) **35**: 1881. 1928.

A description is given of a case of adrenal virilism in a 34-year-old woman. There were typical modifications in the voice and the temperament, and an increased libido. A large neoplasm in the right adrenal region was responsible.—G. Coronedi.

The effects of intense x-ray irradiation of the suprarenal gland. Rogers, F. T. and C. L. Martin, Am. J. Physiol. **93**: 684. 1930.

The direct application of x-rays of an intensity estimated as three and one-half human erythema doses to the one exposed adrenal gland of dogs, after the excision of the other gland, produced no subsequent changes in the gland, except a slight fibrosis. No functional disturbances appeared in these animals during a period of observation of from 3 to 12 months after the irradiation. The application of six to eight doses to the adrenal gland produced no observable functional disorders in dogs kept three months after irradiation, although fibrous proliferation in the gland can be demonstrated microscopically. Adrenal deficiency symptoms can be induced in dogs by the surgical excision of one gland and giving excessive x-ray doses to the remaining gland, but the lapse of several months may be required for their appearance. These effects are as follows: the gradual onset of a progressive muscular weakness, depression of metabolism, terminal lowering of the blood chlorides and death. Heavy dosage of x-rays to the exposed adrenal gland induces degenerative changes, first in the medulla of the gland, and then of the zona reticularis and zona glomerulosa and an extensive proliferation of fibrous tissue throughout the gland.—Authors' Abst.

Atrophy of the adrenals associated with Addison's disease. Susman, W., J. Path. & Bact. **33**: 749. 1930.

Five cases of Addison's disease are recorded in which the lesion in the adrenals was a simple or fibroid atrophy, and it is found that about one-fifth of all cases of Addison's disease are associated with this form of lesion. Atrophy of the adrenals as a cause of Addison's disease appears to be more common in England than elsewhere. In cases of atrophy, both cortex and medulla are usually affected, but a lesion of the cortex is the more constant and may be the sole feature in some cases.—Author's Summary.

Addison's disease in a Negro. Report of a case. Sala, A. M. and M. Jacobi. Arch. Int. Med. **46**: 375. 1930.

Including the present one, only five cases of tuberculous involvement of the suprarenal glands in Negroes are on record, a rather surprising fact in view of the frequency of pulmonary and miliary tuberculosis in the race. In this

series of cases, females were more frequently affected than males (3:2), as against an average of (2:1) greater frequency in males among white people. The age incidence in these cases was somewhat higher than in white people. Pigmentary changes did occur in the cases of considerable duration. These involved areas usually uninvolved in white people (nail-beds, soles and palms), although this distribution may be due merely to the more ready recognition of pigmentary changes in these areas in colored patients. Changes in general pigmentation may become extreme and extensive. In the acute forms, pigmetary changes may be absent. The course in the cases recorded was more rapid than in white people. Nervous symptoms were not prominent in any case. Laryngeal symptoms—hoarseness, pain on speaking and a choking sensation—were prominent, or even presenting, symptoms in this group of cases. No local evidence to explain these symptoms was present. Asthenia was a prominent symptom; anorexia was marked. In all cases, except in those in which pigmentary changes and gastro-intestinal and asthenic symptoms were marked, the diagnosis, always difficult to make in white people, was extremely difficult; in the acute case, it was not often made except at autopsy.

—Authors' Summary.

Adrenalectomy and muscle fatigue. Stevens, H. C. and J. M. Rogoff. Am. J. Physiol. **93**: 691. 1930.

Experiments were made upon decerebrate, adrenalectomized cats, in which the fatigue curve of the gastrocnemius muscle was studied. Curves obtained during the period of survival in good health, following double adrenalectomy, did not differ materially from curves obtained with animals that were not subjected to adrenalectomy. The behavior of cats during the following decerebration, the blood pressure and respiratory response, the specific reactions of the gastrocnemius muscle as evidenced by the fatigue curve, the component phases of the twitch myogram and the chronaxie of the tibial nerve and the muscle in the adrenalectomized cats were compared with similar observations, made under the same conditions, in control non-adrenalectomized animals.

—Authors' Abst.

Studies on suprarenal insufficiency. VIII. The blood volume of the rat in suprarenal insufficiency, anaphylactic shock and histamine shock. Wyman, L. C. and Caroline tum Suden. Am. J. Physiol. **94**: 579. 1930.

In 23 normal rats the per cent of plasma of the blood was from 51.7 to 60.7, averaging 56.3 per cent. The blood volume was from 6.6 to 9.6 per cent of the body weight, averaging 7.6 per cent. Following a control blank operation blood volume determinations were within the normal range. In suprarenalectomized rats having autoplastic cortical transplants but no demonstrable chromaffin tissue blood volume determinations were within the normal range. In suprarenalectomized rats which possessed gross accessory cortical tissue and before the appearance of severe symptoms in those which died later of insufficiency the blood volume remained unchanged except for normal fluctuations. After severe symptoms of suprarenal insufficiency had appeared or during the final stages of insufficiency there was a reduction in the blood volume, due chiefly to a reduction in the plasma volume. It is suggested that inability to maintain capillary tone and normal permeability, probably due to lack of medullary suprarenal secretion, and resulting in reduction of plasma volume, is the chief factor in increased susceptibility of suprarenalectomized rats to anaphylactic and histamine shock.—Authors' Summary.

Metabolism in dementia praecox. Stevenson, G. H. and J. C. Thomas. Canad. M. A. J. **22**: 636. 1930.

Study of 16 cases showed no constant or definite deviation from normality.—A. T. C.

Pathological precocities (Precocita patologiche). Antognetti, L. Endocrinol. e patol. constit. **4**: 297. 1929.

Five cases of precocious sexual development are described, in two of which there was a precocious commencement of the menstrual rhythm with indications of hypothyroidism. Three cases of precocious matronism (Pende's syndrome) are described.—G. Coronedi.

A pressor substance obtained from the prostate gland of the bull. Collip, J. B. Tr. Roy. Soc. Canada (Sect. V, Biol. sc.) **23**: 165. 1929.

An epinephrine-like substance has been demonstrated in extracts made from the prostate gland of the bull. Its preparation is described and effects similar to epinephrine demonstrated as regards blood pressure (and cocaine sensitization) uterine contractions and blood sugar.—R. G. H.

Ovary-stimulating hormone of the placenta. Collip, J. B. Nature, **125**: 444. 1930. Abst., Chem. Absts. **24**: 3824.

Collip describes a crystalline substance obtained from extracts of placenta. It is protein- and lipoid-free and, when given to experimental animals, is active in bringing about prematurity of young rats and in prolonging the gestation period of adult rats. The effect of the extract of placenta is being studied in certain clinical cases.

Effect of ovarian extract on motility of rhythmically contracting uterus. Durrant, E. P. Am. J. Physiol. **93**: 645. 1930.

The rhythmic contractions of excised rat uterus in oxygenated Tyrode's solution were recorded from the entire horn and from ovarian and cervical ends separately. While contracting normally the segments of uterus were subjected to the action of 0.1 per cent, 0.2 per cent and 0.3 per cent of different commercial ovarian extracts. Of 13 animals thus studied, all but one responded with diminished activity up to complete inhibition with the largest dosage. Similar dosage had no effect on segments of intestine from the same animal. —Author's Abst.

Effects of ovarian extracts on voluntary activity of white rat. Durrant, E. P. Am. J. Physiol. **93**: 646. 1930.

Eighteen mature female white rats were kept in self-registering revolving cages until the cyclic variations in activity associated with oestrus were clearly shown on graphs prepared from the daily runs. One-half were then injected subcutaneously with 0.2 cc. of a pharmaceutical ovarian extract each day. The other half were similarly treated with distilled water. The treatment, continued for 24 days, was without effect on the rhythm of activity but produced a marked disturbance in the vaginal mucosa.—Author's Abst.

Multiple ovaries and oestrus. Friedman, J. L. and L. B. Nice. Am. J. Physiol. **93**: 650. 1930.

Twenty-one female white rats each received an ovary from two other white rats so that each animal had four ovaries—its own pair and one from each of two others. The oestrus of these rats was studied by the smear method before and after transplantation. After transplantation the cycles were found irregular and much more frequent than before. The activity of these rats does not correspond closely to the oestrus cycle.—Authors' Abst.

Influence of follicular and corpus luteum hormones on the uterine endometrium of rabbits and monkeys. Hisaw, F. L., R. K. Meyer, S. Leonard and H. L. Fevold. Am. J. Physiol. **93**: 659. 1930.

Extracts of sow corpora lutea yield a crystalline and a non-crystalline fraction which produce characteristic physiological reactions in experimental animals. The crystalline fraction causes relaxation of the pelvic ligaments of castrated female guinea pigs while the non-crystalline fraction promotes several reactions generally accredited to the corpus luteum, two of which are the development of the progestational endometrium in the uterus of castrated rabbits and the premenstrual endometrium in the uterus of castrated monkeys. Relaxation as well as progestational and premenstrual changes in the uterine endometrium require the action of both the follicular and corpus luteum hormones, neither being able to elicit positive results in castrated animals when given alone. Neither can the corpus luteum hormones promote and preserve the relaxed, progestational, or premenstrual conditions over an extended period in the absence of the follicular hormone. The corpus luteum hormone alone

will not prevent menstruation in a castrated monkey previously treated with follicular hormone nor prevent the return of the progestational endometrium of a rabbit to a castrated condition. These reactions seem to be of a "one two" nature, i.e., the follicular hormone must act first, followed by the corpus luteum hormone, and both must be present to prolong the effect. The crystalline fraction of the corpus luteum which produces the relaxation of the pelvic ligaments of the guinea pig bears a qualitative relationship to the follicular hormone, while the non-crystalline fraction which produces the uterine changes bears a quantitative relationship to the oestrus producing hormone. That is, large doses of follicular hormone do not inhibit the action of the relaxative hormone, but in the case of the non-crystalline fraction large doses of oestrin will prevent its action on the uterus.—Authors' Abst.

The relation of gonadal condition to erythrocyte number in fowls. Juhn, Mary and L. V. Domm. Am. J. Physiol. **94**: 656. 1930.

The erythrocyte number was determined in 80 brown leghorns, 40 males and 40 females, at intervals from the day after hatching to 16 months of age. A definite sex dimorphism in the number of red cells was noted confirming other observations cited. The juvenile and the gonadectomized bird of either sex and the mature female all show a similar erythrocyte number. The number of red cells is significantly higher in the adult male, the increase becomes apparent at the time of sexual maturity. Thirty red counts carried out in poulards show that the modifications in the male direction noted after removal of the left ovary can now be extended to include the erythrocyte number which equals that of the adult male.—Authors' Summary.

Ovarial function and lipoid content (ovarialfunktion und Lipoidhaushalt; über die Verteilung des Blutcholesterins in fréies und verestertes Cholesterin in den verschiedenen Funktionsphasen der Keimdrüse; der Gesamtfettsäuregehalt des Blutes bei regelmässiger, bei unregelmässiger und fehlender Ovarialfunktion). III. Kaufmann, C. and O. Mühlbock. Arch. Gynäk. **139**: 254. 1929. Abst., Chem. Absts. **24**: 3545.

During menstruation the total cholesterol content of the blood serum decreases, and the change is due largely to a decrease in free cholesterol. There are also changes in the relation of cholesterol esters to free cholesterol. At the time of menstruation 85-90 per cent of the total cholesterol is in the ester form and at other times 70 per cent. The free cholesterol also shows a greater variation than the cholesterol in ester form. The lecithin content of the blood serum is independent of the cholesterol content and does not show any definite alterations during menstruation. Increased amounts of total fatty acids are noted in the circulating blood during menstruation. Removal of the ovaries does not produce a regular alteration in the total lipoid content of the blood serum or of the distribution of the individual components. In the physiological climacteric increased cholesterol, lecithin and fatty acid content of the blood serum are occasionally noted.

A new demonstration of physiological activity of corpus luteum. Macht, D. I. Am. J. Physiol. **93**: 671. 1930.

It has been pointed out by Siddall and others that the weight of the uterus in the white mouse bears a definite ratio to the weight of the adult, non-pregnant animals, this ratio being over 400. Frank and other investigators have found that when white mice are given injections of the follicular hormone, the uterus is hypertrophied, and Siddall established that in such cases the ratio of the weights of the uterus and the whole animal is much below the normal ratio 400. In the present investigation, the writer attempted to determine whether the corpus luteum hormone would counteract the effects of follicular hormone on the size and weight of the uterus. Three sets of experiments were carried on simultaneously. In the first set, mice were fed a normal diet without the administration of ovarian extracts. In the second set, mice were given the same food but received a number of injections of the follicular hormone. In the third set, mice were injected simultaneously with the follicular hormone and corpus luteum extracts. After various periods of time, ranging from 10 days to two weeks and more, the animals were killed, the uteri dissected, and the relation of the uterine weight to the weight of the whole animals was

determined. In the normal controls, this ratio was never below 400 and was usually higher than that figure. In the mice which received injections of follicular extracts alone, a definite hypertrophy of the uteri was noted in most cases, and the ratio of the uterus to the body weight was much below 400. In the third set of experiments the mice which received simultaneous injections of the follicular and corpus luteum extracts showed no hypertrophy of the uteri and gave the same ratio of the weights as the normal controls. Such triple sets of experiments were performed many times, always giving the same results. It therefore appears that injections of corpus luteum extracts counteract the hypertrophy-producing effects of follicular extracts. Feeding experiments with the ovarian products were also conducted and gave similar results, although a much longer period of time was necessary.—Author's Abst.

Studies of female genital hypoplasia. Meaker, S. R. J. A. M. A. **95**: 468. 1930. Abst., A. M. A.

The author asserts that female genital hypoplasia is a common condition and a major factor in the causation of sterility. The immediate cause of such hypoplasia is most commonly a conpubertal insufficiency of the anterior lobe of the pituitary. The diagnosis of established hypoplasia in adult women depends mainly on pelvic examination and the recognition of characteristic stigmas in the uterus. Treatment of established genital hypoplasia is at the present time wholly ineffectual. The diagnosis of incipient or threatened hypoplasia in adolescent girls depends, first, on the recognition of abnormal menstrual behavior, and, secondly, on the identification of depressing constitutional factors, both endocrine and non-endocrine. The treatment of incipient or threatened hypoplasia consists in the elimination of all depressing constitutional factors, and is a hopeful undertaking. In the management of the adolescent cases there exists a new and important opportunity for the practice of preventive gynecology. Both non-endocrine and endocrine abnormalities require to be corrected. The general hygiene of the modern girl leaves much to be desired. Milder grades of anemia are frequent and appear to have a particular depressing effect on the reproductive system. Chronic focal infection contributes demonstrably to disturbance of the endocrine functions. In occasional cases congenital syphilis, rickets, lesions of the central nervous system, and other disease entities require treatment on the ground of their harmful influence on the metabolic level, as well as on their own merits. The mechanism of endocrine treatment in the adolescent patient is primarily substitution, with an excellent chance of secondary homostimulation. Monoglandular therapy gives better results than pluriglandular; if the primary focus of failure is normalized, responsive disturbances in other glands tend to regulate themselves. The gland required is usually the anterior lobe of the pituitary, occasionally the thyroid, and never the ovary. Success depends on the use of potent preparations in adequate dosage.

The effect of testicular extracts on the blood calcium. Mirvish, L. and L. P. Bosman. Brit. J. Exper. Biol. **6**: 355. 1929. Abst., Physiol. Absts. **15**: 316.

Injection of alcoholic extract of testis equal to about 200 gm. fresh tissue, lowers the calcium content of rabbit blood by about 30 per cent. The character of the fall is the same as that obtained after ovarian injection, though the amount required is about 10 times greater. When the extract was purified with ether, no fall was recorded. It is suggested that the presence of such a physiological reaction might be utilized to extract and purify the testicular hormone.

Ovarian reaction in young rat to action of urine of pregnant women. Malinengo, L. Clin. ostet. **32**: 385. 1930. Abst., J. A. M. A. **95**: 1215.

The degree of reaction of the ovary of the young rat to the action of the urine of a pregnant woman is, within strict limits, parallel to the dose of the injected substance. The possibility of securing with small doses of urine a follicular phase, and with heavy doses massive hyperluteinization of the ovary, awakens doubt as to the correctness of the principles on which Evans and Simpson base their theory in regard to the plurality of antehypophyseal hormones.

The preparation of the crystalline follicular ovarian hormone: Theelin. Veler, C. D., S. Thayer and E. A. Doisy. J. Biol. Chem. **87**: 357. 1930.

A quantity production procedure for the preparation of theelin is described. Essentially the procedure depends upon the fact that theelin, which behaves as a very weak acid, may be extracted from organic solvents with dilute NaOH solutions, and then in turn may be extracted from the alkaline solution by certain organic solvents.—Authors' Summary.

Preparation of female sex-hormone (Zur Darstellung des weiblichen sexual Hormons). Zondek, B. and C. van Eweyk. Klin. Wchnschr. **9**: 1436. 1930.

Two methods of separating the hormone from pregnant urine (a) absorption with charcoal and (b) precipitation by salts of a heavy metal, lead acetate for example, are described. A larger degree of recovery is had by the second method. By repeated solution and evaporation the hormone can be highly purified and so concentrated that 1 cc. of a watery solution may contain as much as 8000 oestrus producing units.—E. P. D.

Influence of lipoid hypophyseal hormone on deaminization in the organism (Über den Einfluss eines lipoiden hypophysären Hormons auf die Desaminierungsprozesse in den Organen). Agnoli, R. Arch. f. experi. Path. u. Pharmakol. **134**: 74. 1928. Abst., Biol. Absts. **3**: 1196.

The rate of deaminization in animals was determined by estimating the amount of amino acids in the blood after intravenous injection of known amounts of glycocoll. An extract of posterior lobe of the hypophysis (ox) had no influence on the process. Commercial extracts (hypophysin of Höchst and endopituitrin of the Serotherapeutic Institute of Milan) were similarly without effect. Fresh extract of the whole gland (ox) had a definite action on the process, deaminization undergoing a noticeable acceleration. Lipoid extracts of whole dried gland (ox) and fresh gland (swine) exhibited a more marked accelerating action. There must be a hormone in the anterior lobe of the hypophysis, perhaps corresponding to the so-called thetelin of Robertson, which possesses a stimulating action on intermediate protein metabolism.

The influence of different parts of the hypophysis upon size growth of Rana tadpoles. Allen, B. M. Physiol. Zool. **1**: 143. 1928. Abst., Biol. Absts. **3**: 1197.

Living anterior, intermediate, and posterior lobe material of the hypophysis of adult frogs was implanted separately into thyroidectomized and into hypophysectomized tadpoles of the same species, Rana aurora draytoni. The anterior lobe of the hypophysis is shown to be alone concerned in stimulating growth. It causes the hypophysectomized tadpoles to attain normal size even though previously much retarded. Implantation of the intermediate or posterior lobes of the hypophysis into hypophysectomized tadpoles does not cause them to resume normal growth. Implantation of the anterior lobe of the hypophysis into thyroidectomized tadpoles causes them to show a normal growth rate only slightly greater than that shown by normal controls or thyroidectomized tadpoles into which such implantation has not been made. These results were not due to nutritional absorption of the implant, because the latter was maintained in a living and functional condition and because implants of intermediate and posterior lobe of the hypophysis and of liver failed to stimulate growth, in spite of the fact that the intermediate lobe at least showed its activity by producing very striking color changes.

Diabetes insipidus during pregnancy. Anselmino, K. J. and F. Hoffmann. Zentralbl. f. Gynäk. **54**: 2061. 1930. Abst., J. A. M. A. **95**: 1388.

Anselmino and Hoffmann report a case in which diabetes insipidus became manifest in two successive pregnancies and disappeared again during the first day of the puerperium. The diagnosis diabetes insipidus was based on the determination of the sodium chloride content of the blood and of the urine during thirst periods and during water tests. The examinations of the blood and of the urine revealed that this case of diabetes insipidus was of the type that is characterized by hypochloremia and hyperchloruria. On the basis of the Hann-Jacobi theory, according to which diabetes insipidus is due to a dis-

turbance in the equilibrium between the secretions of the anterior lobe of the hypophysis and its posterior lobe (an excessive secretion of the anterior lobe causes diabetes insipidus) the authors reason that in this case the isolated manifestation of the disease during two gravidities may be explained as follows: A syphilitic infection caused a functional deficiency of the posterior lobe. Under ordinary conditions this deficiency was latent. However, during pregnancy the functional capacity of the organ was taxed more and the deficiency became manifest.

Hypopituitarism with special reference to its sexual manifestations. Berry, N. E. Canad. M. A. J. **22**: 354. 1930.

A report of a case of Froelich's syndrome.—A. T. C.

Galactorrhea in acromegaly (Galactonhée chezune acromégale). Carnot, P. and Bouttier. Bull. et mém. Soc. méd. d. hôp. de Paris, **54**: 392. 1930. Abst., J. A. M. A. **94**: 2028.

In Carnot and Bouttier's patient, aged 27, symptoms of increasing acromegaly had been noted for several years. The symptoms consisted of an increase in the size of the hands and feet, severe pains and increasing size of the maxilla, hypertrophy of the tongue, enlargement of the sella turcica, and thickening of the bones of the skull. Menstruation had been irregular and often deficient for the past three years, coincident, however, with a persistent lactic secretion from the breast. Injection of the urine of the patient into not fully developed or castrated female mice and rats and male rats did not stimulate the development or activities of the genitalia or hormones of hypophyseal origin. According to the authors, this points toward separate kinds of hormones. Anterior lobe hormones stimulating mammary secretion may be distinguished from those stimulating activity of the genito-urinary tract.

The functions of the pituitary in the dog. II (Experimentelle Untersuchung der Hypophysenfunktion beim Hunde-II). Koster, S. Arch. f. d. ges. physiol. **224**: 212. 1930. Abst., Physiol. Absts. **15**: 313.

The endocrine glands were examined in dogs in which the pituitary had been removed (experiments previously reported). The thymus was rather heavier than normal, and the suprarenals showed no definite changes in weight. All the other endocrine organs were smaller and lighter than in control animals.

The effects of extracts of the posterior hypophysis on the water interchange in muscle. Steggerda, F. R. Am. J. Physiol. **93**: 691. 1930.

Measurements were made on the effects of surgical pituitrin, vasopressin and pitocin on the water interchange of the isolated frog's gastrocnemius muscle. In all cases the left gastrocnemius served as the experimental muscle, whereas the right gastrocnemius of the same frog was the control. After isolation, both the right and left gastrocnemius muscles were placed in normal Ringer's solution for one-half hour. Weighings of the muscles were then made on an analytical balance, after which the muscles were submerged in Ringer's solutions of various strengths. In all cases extracts of posterior pituitary were added to the solution containing the experimental muscle. Successive weighings were made at intervals over a period of more than two hours, whereby percentage variations in muscle weights could be noted and plotted. Ninety experiments were performed, using normal, hypotonic and hypertonic Ringer's solutions containing different amounts of surgical pituitrin, vasopressin and pitocin. Plotted curves show no appreciable change in weight between the experimental and control muscles. The results tend to show that extracts of the posterior hypophysis have no effect on the permealibility of the isolated frog's gastrocnemius to water.—Author's Abst.

Use of extracts from posterior lobe of hypophysis in local anesthesia (Über die anwendung von Hypophysenkenterlappenextrakten in der Lokalänasthesie). Wermer, P. Klin. Wchnschr. **9**: 779. 1930. Abst., J. A. M. A. **95**: 308.

Wermer points out that in local anesthesia cocaine or procaine hydrochloride is usually combined with epinephrine. But because epinephrine frequently causes complications the author made tests to determine whether this

suprarenal extract could be replaced by extracts from the posterior lobe of the hypophysis. He described his experiments and then he relates that this mixture of procaine hydrochloride with the extract from the posterior lobe of the hypophysis was successfully employed for local anesthesia, especially in laryngologic operations, in tonsillectomy and in dentistry. It has also been used in resection of the stomach. Among the patients on whom the hypophyseal extract was employed were several with endocarditis, valvular defects, hypertension or hyperthyroidism and also numerous patients who were more than 70 years of age. For surgical interventions the dosage is from 5 to 10 Vögtlin units of hypophyseal extract to 250 cc. of a solution of procaine hydrochloride; for tonsillectomies from 1 to 3 units for 30 cc. of procaine hydrochloride solution; and in dentistry ½ unit for 2 cc. or a 2 per cent solution. The hypophyseal extract contracts the capillaries mainly. Complications did not develop. Their absence was especially noticeable in dentistry and in laryngologic operations. Many dental patients in whom epinephrine had always caused unpleasant manifestations found the mixture of procaine hydrochloride with hypophyseal extract entirely agreeable. In major operations the patients are not troubled by palpitation of the heart, and the pulse rate sometimes even shows a decrease. Intestinal complications were likewise absent. The author recommends the use of hypophyseal extract in all forms of infiltration and regional anesthesia. He considers it especially valuable in cases in which the suprarenal extract is contraindicated on account of its influence on the circulation and on the metabolism.

The hormones of the anterior pituitary. IV. Preparation of follicle-maturing hormon (Prolan A). Method of clinical urine analysis as a test for Prolan (Ueber die Hormone des Hypophysenvorderlappens. IV. Darstellung des Follikelreifungshormons (Prolan A). Metodik der Klinischen Harnanalyse zum Nachweis des Prolan). Zondek, B. Klin. Wchnschr. **9**: 1207. 1930.

Urine is acidified with acetic acid precipitated with 96 per cent alcohol and the precipitate purified by ether. The ether is removed and the purified precipitate dissolved in water. The dissolved substance is then further treated with alcohol and ether until a high degree of purification is reached. Biological tests based on the characteristic reactions of the ovary show that Prolan can be obtained from both non-pregnant and pregnant urine.—E. P. D.

The effect of cholecystokinin on the human gall bladder. Ivy, A. C., G. E. Drewyer and B. H. Orndoff. Am. J. Physiol. **93**: 661. 1930.

A "purified" solution of cholecystokinin (1860 preparation) was prepared and shown to be neither toxic in the dog nor antigenic in the guinea pig. It was free of vaso-dilatin and active in the dog in 3 mgm. doses. From 25 to 30 mgm. of this material has been injected intravenously at ten-minute intervals into 5 normal subjects and 3 dispensary patients in which gall-bladder disease had been suspected. The gall bladder was visualized with phenoltetraiodophthalein; of the 5 normal subjects, all but one manifested some degree of gall-bladder evacuation when injected every 10 minutes for one hour. On one the evacuation was complete, in the other three it was partial. Two of the 5 felt "light-headed" about one hour after completing the injections, which sensation disappeared within the course of 30 minutes, no other symptoms being complained of. Only 3 doses were given at 10-minute intervals to the three dispensary patients. Two of the 3 showed a definite decrease in the size of the gall-bladder shadow, one of them having a pericholecystitis. Further work on the human will not be undertaken until the product is further purified.
—Authors' Abst.

The surigcal problems presented by the diabetic. Bazin, A. T. Canad. M. A. J. **23**: 146. 1930.

Provided that the diabetic state is recognized and properly controlled, diabetes does not influence the surgical treatment and prognosis. In the Montreal General Hospital in 1929 the diabetics showed 221 cases exhibiting complications and associated conditions. Of these 87 were surgical and 73 went to operation. There were 2 deaths. The importance of accurate biochemical studies during control is emphasized. Control by urine analysis is imperfect and often inadequate, as is also determination of a fasting blood sugar. A blood sugar time curve is necessary.—A. T. C.

A brief review of certain physiological properties of insulin. Best, C. H. Canad. M. A. J. **23**: 141. 1930.

The review deals with the following: site of production; liberation; action; interference with the action; preparation and properties; and insulin and diabetic mortality.—A. T. C.

Clinical functional test of the islands and the question of insular genesis of obesity (Zur klinischen Funktionsprüfung des Inselapparates und zur Frage der insulären Genese der Fettsucht). Depisch, F. and R. Hasenöhrl. Klin. Wchnschr. **9**: 215. 1930.

The work is based on the observations of Aschner that the difference between capillary and venous blood sugar after a glucose meal represents the insulogenic function and also the ability of the tissues to use glucose; thus the difference between these two levels should be the functional capacity of the islands. The authors state that contrary to Aschner, the niveau difference has not a special significance. In animals with extirpated pancreas, thus a high blood sugar, after insulin injection the venous sugar rises due to washing out from the tissues so that it rises even above the arterial. The question of obesity the authors feel cannot be explained wholly by increased insulogenic function.—H. J. J.

A preliminary note on the detection of an insular hormone in the duodenum. Laughton, N. B. and A. Bruce Macallum. Canad. M. A. J. **23**: 348. 1930.

Confirming Heller the authors find that injection of extracts of duodenal mucosa into normal rabbits and dogs prior to injection of half a gram of glucose per kilo body weight lessens the usual degree of hyperglucaemia. It has no effect on the blood sugar of depancreatized dogs with marked hyperglucaemia, so that the extracts do not contain insulin. Since pure secretin has no such effect, and insulin is excluded, there would appear to be a substance in normal duodenal mucosa which stimulates the production of insulin. This suggests that insular failure may result from excessive stimulation of the islets by the duodenal hormone produced as a result of excessive sugar intake over long periods, and secondly, that inflammatory conditions in the duodenum may lead to a deficiency in the hormone followed by diminished activity in insulin output whence a hyperglucaemia. The extract is water-clear and gives none of the protein color reactions.—A. T. C.

The action of intravenous sugar injections on ketonuria in diabetes mellitus and in diabetic coma (Ueber die Wirkung von intravenösen Zuckerinjektionen auf die Ketonurie bei Diabetes mellitus und bei diabetischem Koma). Lorant, J. S. and E. Froehlich. Klin. Wchnschr. **9**: 213. 1930.

Intravenous injection of sugar causes a considerable rise of ketone bodies in diabetics also in coma which persists at least for two hours. The author explains this rise by the transport of the ketones through the injected solution. The author thinks that these injections in coma are bad in so far as they prolong the desugarization and force one to use larger insulin doses, which in turn might cause hypoglycemia together with the first point mentioned.
—H. J. J.

Clinical investigations into the effect of intravenous injections of insulin. II. Hypoglycemic symptoms in normal individuals. Norsted, A., A. Norgaard and Th. E. H. Thaysen. Acta med. Scandinav. **73**: 125. 1930.

Prominent among the hypoglycemic symptoms are the rise of systolic and fall of diastolic blood pressure, and the increase of pulse rate. The maximal changes in blood pressure and pulse rate are found near the time when the hypoglycemia comes to a stop and the blood sugar concentration begins to rise. A very essential—probably the most important—part of this regulation mechanism is very likely an increased activity of the adrenals. It may be that other endocrine glands take part in this regulation, too. The term "insulinism" is perhaps preferable to "hypoglycemic" symptoms.—Authors' Summary.

An investigation of the antagonism of insulin by posterior pituitary extracts as indicated by changes in gastro-intestinal motility. Quigley, J. P. and B. O. Barnes. Am. J. Physiol. **93**: 682. 1930.

Employing unanesthetized trained dogs, fasting 20 to 44 hours, the motility of the stomach and colon has been followed by the balloon method. Using highly purified insulin, confirmation has been obtained of a number of the effects on gastro-intestinal motility previously noted from commercial insulin. The effect of pituitrin (Parke, Davis & Co.), oxytocin or vasopressin on gastro-intestinal motility in insulinized or non-insulinized dogs appears to be entirely similar. The optimal dose for the gastric effect is 4 to 8 units intravenously or any of the pituitary preparations. When administered to animals with low spontaneous tone, high spontaneous tone or the hyperactivity of the gut produced by insulin, complete inhibition of tone and motility was the invariable result. The inhibition began 15 to 20 seconds after the administration of the pituitrin. In animals under the influence of insulin the blood sugar level remained constant for 3 to 5 minutes after the injection of pituitrin but rose to or above normal within 10 minutes. The blood sugar fell in the period which followed, during which the gut was recovering from the inhibition. No indication of an augmentation of gastro-intestinal motility was obtained as the result of the administration of pituitary preparations. The mechanism by which pituitrin inhibits the motility of the gut does not appear to be related to its action on carbohydrate metabolism except during the latter part of the inhibition period.—Authors' Abst.

The diagnosis of renal glycosuria. Rabinowitch, I. M. Canad. M. A. J. **22**: 329. 1930.

During the previous 12 months 3 patients with advanced diabetes were admitted to the Montreal General Hospital; in each case a diagnosis of renal glycosuria had been made less than 2 years previously, in one based upon a sugar time curve made in a hospital. It is considered that for an absolutely correct diagnosis of renal diabetes the following conditions should be fulfilled: There must be no signs nor symptoms of diabetes; there should, ideally, be no family history of diabetes; the figure for blood sugar obtained in the fasting state must always be normal; there must be little or no relationship between the intake and excretion of sugar; the rate of utilization of sugar should be normal; and the individual must not subsequently develop diabetes. Study of a case fulfilling all these conditions is detailed. It is considered that it is unwise to make a diagnosis of renal glycosuria in office practice, and that it is safer to underfeed a normal individual than to overfeed a diabetic. An individual with glycosuria should be regarded as a diabetic until proved otherwise.
—A. T. C.

Lipodystrophy from insulin injections. Reed, Lucille L., W. E. Anderson and L. B. Mendel. J. A. M. A. **95**: 395. 1930. Abst., A. M. A.

In an effort to determine whether injections of insulin or other substances would cause a lipodystrophy, the authors injected healthy female rats subcutaneously in a pad of fat occurring on the ventral surface of the right leg with 0.6 unit of insulin daily, the dose being divided into three parts. (This dosage is on the basis of 3 units per kgm. of body weight, or 210 units for a 70 kgm. man.) Another group of rats was injected with the same volume of physiologic solution of sodium chloride at the same time in the same location. Still another group received no injections at all. The rats were killed after sixty days and the pelt removed. The amount of subcutaneous fat around the right and left legs was estimated separately for the rats in each group by the method described by Reed, Yamaguchi, Anderson and Mendel for the determination of the fat content of adipose tissue. The variations occurring in the groups injected with insulin or with physiologic solution of sodium chloride suggested that neither substance was influential in changing the amounts of fat stored in the subcutaneous tissues. It is conceivable that the adipose tissues of normal and diabetic organisms react differently to injections of insulin or that in the present instance the injections were discontinued before the lipodystrophy had time to develop. In any event the current hypotheses for the genesis of localized lipodystrophy after insulin injections have not been substantiated under conditions that may be regarded as sufficiently drastic to produce the expected results.

Isolation of a new hormone of the pancreas (Isolement d'une nouvelle hormone pancréatique). Santenois, D., H. Verdier and M. Vidacovitch. Rev. franç. d'endocrinol. **8**: 204. 1930.

Working on dogs, over several years and with as rigid experimental discipline as possible, the authors have shown that the pancreas secretes a regulatory hormone affecting the functional activity of the pneumogastric centers. This hormone is found not only in the gland itself and in the blood coming from the gland, but also in the arterial blood of the general circulation. The vagotonizing ability does not belong to insulin but to another hormone secreted by the pancreas. Insulin does not excite the pneumogastric reflexes. The authors were able to extract this vagotonizing hormone of the pancreas, and separated it by the use of alcohol and neutral salts from insulin. They propose to name this substance, at least provisionally, vagotonine. It would appear that the pancreas, through this agency, exerts an important regulatory action on the functional activity of the pneumogastric centers. Resulting from this there is a whole series of physiological actions of vagotonine causing a principle rôle to be attributed to the pancreas in the regulation of activity in different organs innervated by the pneumogastric.

—Authors' Summary—translated.

The alterations in the blood sugar following reflex vagus stimulation (Die Zunahme des Insulingehaltes des Blutes nach reflectorischer Vagus-reizung). Van Goor, H. Arch. néerl. de physiol. **14**: 534. 1929. Abst., Physiol. Absts. **15**: 309.

Stimulation of the nasal mucosa of rabbits by cigar smoke or rebreathing in man may produce a fall of blood sugar lasting some hours. Insulin was estimated in blood by Ahlgren's method, which depends on the time of reduction of methylene blue in presence of glucose and muscle tissue; mean concentrations of insulin (diluted commercial solution was used) decrease the reduction time, as also does serum after reflex vagus stimulation, including rebreathing. Adrenaline, but not phloridzin, produces a shortening also, but both prevent the insulin reduction, though adrenaline plus insulin without glucose show some shortening. Adrenaline plus phloridizin plus insulin shorten, but not in the absence of glucose. Pituitrin causes shortening also and aids the action of insulin.

The parathyroid and ergosterol hypercalcaemia (Nebenschilddrüsenhormon und Ergosterin-hypercalcamie). Bischoff, G. Ztschr. f. phys. Chem. **188**: 247. 1930. Abst., Physiol, Absts. **15**: 315.

Administration of the parathyroid hormone to dogs with hypercalcaemia from overdoses of ergosterol led to a definite fall in the serum calcium. This fall lasted about as long as the rise in serum calcium lasts in normal animals given parathyroid. The premortal fall in serum calcium which occurs with large overdoses of parathyroid hormone in normal animals occurred also in animals suffering from ergosterol poisoning sooner and with smaller doses of parathyroid. If the parathyroid is given in the early stages of ergosterol poisoning, the high serum calcium fall and is kept at the low level for some 24 hours before a rise again occurs, the condition of the dogs being much improved. The parathyroid hormone can thus cause and maintain a lowering of blood calcium under some conditions.

Bone changes in hyperparathyroidism. Compere, E. L. Surg. Gynec. & Obst. **50**: 783. 1930.

A case is reported in which a diagnosis of hyperparathyroidism was made on the basis of a syndrome consisting of pain and bowing of the bones of the weight-bearing extremities, osteoporosis of the bones of the skeleton, progressive muscular weakness, elevated serum calcium and lowered serum phosphorus, a negative calcium balance, and a palpable nodule in the lower pole of the right lobe of the thyroid gland. An enlarged adenomatous parathyroid gland was removed at operation and a second gland was removed from the opposite lobe of the thyroid gland and found to be normal. Symptomatic improvement followed resection of this tumor. A résumé of 11 other cases which may be included under the definition of hyperparathyroidism and which have been recently reported, is included. All of the cases were characterized by

generalized osteoporosis. Areas of rarefaction resembling bone cysts were reported in 6 of these cases and in 3 cases diagnoses of giant cell tumors were made. Spontaneous fractures had occurred in 5 of the cases. Tumors of the parathyroid glands were removed at operation from 8 of these patients and, in another case where no tumor was found, two normal glands were removed. One patient died in tetany after removal of a parathyroid tumor and one normal parathyroid gland. Symptomatic improvement was noted in all of the other cases, after removal of the parathyroid tumor. In 4 of these cases the authors reported roentgenological evidence of increased density of the bones of the skeleton. The symptomatic improvement in these cases, the chemical evidence of increased calcium retention, and the x-ray evidence of increased density of the bones in a few cases which had been followed for a long period after operation are results which, as the operative risk is slight, do justify surgical intervention in cases such as that reported here.—Author's Abst.

The effect of parathyroid hormone and calcium lactate on calcification in pulmonary tuberculosis. Gordon, B. and A. Cantarow. Am. Rev. Tuberc. **20**: 901. 1929.

Parathyroid extract was administered to 60 tuberculous patients to determine the effect upon symptoms, calcification and the course of the disease. Treatment varied from a few days to five months. Roentgen-ray observations, blood calcium and blood clotting determinations, strength tests, laryngeal examinations, and records of weight, temperature, pulse rate and blood pressure were made. Subjective observations were limited to the occurrence of symptoms. In most instances an increase in blood calcium was maintained. There seemed to be a favorable influence upon strength and on vague muscular pains. Cough and the amount of sputum were diminished in 34 patients; pain of acute pleurisy was relieved in 14 patients and in several instances a decidedly favorable effect upon hemoptysis occurred. There was no apparent change in the activity of the tuberculous processes, except possibly a decrease in exudate. Nineteen patients in the group were observed for three years since cessation of treatment. Calcification occurred in three patients and fibrosis was noted in four instances, but these individuals appeared to have natural tendency to heal. Four patients showed an extension of the disease and the remaining number suggested no definite change. Twenty-nine patients had died and twenty had not been traced. In seven patients examined at necropsy there was no evidence of calcification that would not be expected in the usual process of healing. Since the use of parathyroid extract apparently failed to influence calcification, further studies were made to determine the effects of calcium lactate administered in addition to parathyroid extract. Roentgen-ray studies of the lungs and bones of the hands were made before treatment was instituted for comparison with roentgenograms taken every two weeks during the course of treatment. There was no evidence of calcification or decalcification in the lungs or bones. Symptomatic manifestations, especially 4-8 hours after the administration of parathyroid hormone, were similar to those noted in the first group of patients. The study suggests that the administration of calcium salts and parathyroid hormone may be of considerable value in relieving symptoms and in decreasing certain exudative processes in tuberculous patients. Obviously these influences may have a favorable action on the course of the disease but there are no data to prove definitely that the procedures cause a deposition of lime salts.—Authors' Abst.

The effects of solar irradiation of long visible and ultraviolet wavelengths respectively, with and without supplementary irradiation of various types, on the growth of chicks and the development of parathyroid glands. Sheard, C., G. M. Higgins and W. I. Foster. Am. J. Physiol. **93**: 686. 1930.

Confinement of chicks behind red-purple corex (Corning Glass G 986 A transmitting 270 to 400 millimicrons) or amber glass (Pittsburgh Amber 48, transmitting 500 millimicrons to end of visible spectrum) does not permit normality in development and growth of chicks or of glands. Normal parathyroid glands develop only in the presence of both the visible and ultraviolet portions of radiant energy. Supplementary irradiation of chicks, housed behind the amber filter, with an air-cooled quartz mercury lamp (ultraviolet irradiation of approximately 575 ergs each second for each square millimeter) for ten to fifteen minutes a day induces normal growth and development of parathyroid glands. Ultraviolet irradiation of the heads only of chicks is appar-

ently as effective as (and possibly more so than) irradiation of the bodies and legs only. The ultraviolet portion of sunlight, as transmitted by corex, is not sufficient to compensate for the absence of vitamin D in the diet or the ultraviolet content of unifiltered sunlight. Microscopic investigations (Becke method) on the calcification of tissues (femurs) in chicks about three and five months old, respectively, kept behind either amber or corex filters and given various supplementary amounts of irradiation with the quartz mercury arc, show that normal calcification does not occur in chicks receiving only the long wavelengths of sunlight. Further evidence is presented to support the statement that normal growth of chicks and development of parathyroid glands are dependent on both the ultraviolet and visible portions of solar irradiation, all other factors remaining constant so far as is known.—Authors' Abst.

Parathyroid tumor and changes of the bones. Snapper, I. Arch. Int. Med. **46**: 506. 1930.

The following points were noted in a patient suffering from extensive decalcification of the bones, combined with violent pain: The illness began as osteitis fibrosa generalisata. Therefore there existed a pseudo-osteomalacic end-stage of Recklinghausen's disease. There was a great increase in the calcium content of the serum. The deviation was considered to be a symptom of hyperfunction of the parathyroids. There was a small swelling in the thyroid. On account of these facts, a tumor of a parathyroid gland was suspected, and was found during operation. After extirpation of this small tumor, clinical recovery occurred.—Author's Summary.

Vasomotor reflexes following parathyroidectomy. Stoland, O. O. and A. M. Lands. Am. J. Physiol. **93**: 691. 1930.

The vasomotor reflexes were studied in dogs and cats under ether or amytal anesthesia before and two to ten hours after the removal of thyroids and parathyroids. After thyroparathyroidectomy there was found an increase in the irritability of the vasomotor centers as shown by an augmented pressor or depressor response. There was a gradual increase in irritability up to a maximum after which the response was diminished approaching the normal. Clamping the veins from the parts stimulated did not alter the response but denervation completely eliminated response. The results indicate that the increased vasomotor responses occurring a few hours following thyroparathyroidectomy is due to increased irritability of the nervous mechanisms involved. No evidence was found in favor of a pressor autocoid substance liberated from the tissues stimulated as suggested by Vincent and Thompson.—Authors' Abst.

The excretion of calcium through the intestine. Taylor, N. B. and A. Fine. Am. J. Physiol. **93**: 544. 1930.

There is a small but constant excretion of calcium through the small and the large bowels of normal cats. Calcium injected into the veins of animals kept upon the usual diet of meat scraps and biscuit practically disappears from the blood within 3 hours. The disappearance cannot be accounted for by excretion through the bowels or kidneys. So far as has been determined, the excess calcium does not leave the body. The excretion of the injected calcium through the large and the small bowels is several times greater in parathyroidectomized than in normal animals. The administration of parathyroid extract was found to be without significant effect upon the excretion of calcium through the bowel during a 6-hour period. This was slightly less than that found in normal animals, but the difference was slight and cannot be considered significant.
—Authors' Summary.

Some effects of the administration of excessive doses of irradiated ergosterol to normal and to parathyroidectomized dogs. Taylor, N. B., H. D. Branion and H. D. Kay. J. Physiol. **69**: 35. 1930.

The normal action of irradiated ergosterol depends on the integrity of the parathyroid glands.—C. I. R.

The chronaxie of the vagus nerve in dogs given methyl guanidine sulphate and in thyroparathyroidectomized dogs. Woodbury, R. A. Am. J. Physiol. **93**: 699. 1930.

The rheobase and chronaxie of the vagus nerve to the heart were determined using 82 stimuli per second during a stimulation period of two seconds. In dogs treated with small doses (10-50 mgm. per kilo) of methyl guanidine sulphate there followed an increased vagus irritability within ten minutes following intravenous injections and in 30 to 60 minutes following subcutaneous injections. Eighty minutes to three hours after the subcutaneous injections the rheobase and chronaxie readings indicate irritability below normal. Larger doses produce decreased irritability followed by increase to above normal. In thyroparathyroidectomized dogs vagus irritability was increased two to four hours after the removal of the parathyroids and continued high during tremors and mild tetany. Following severe tetany or convulsions the increased rheobase and chronaxie readings indicate a fairly marked fall in irritability.
—Author's Abst.

The physiological action of an acid extract of normal thyroid glands with low iodine content. Baker, H. L., C. M. Bacon, C. J. Lundy and D. Klein. Am. J. Physiol. **93**: 630. 1930.

An extract has been prepared from normal thyroid glands, with a low iodine content having the following properties; increases the blood pressure; slows the heart rate; increases blood sugar; lowers the CO_2 capacity of the blood; has no effect on the blood calcium. The rise in blood pressure was secured after vagus section, after atropine, and after the spinal cord had been transected just below the medulla. The slowing of the heart rate was abolished by sectioning the vagi and the use of atropine. Kidney, suprarenal, liver, ovary, pancreas, duodenum, thymus, prostate, spleen and muscle subjected to the same method of preparation did not yield extracts having the properties of the thyroid extract. A depressor substance was found in the same fraction of every tissue studied including the thyroid and excepting the suprarenal gland. The pressor and other properties of the thyroid fraction herein described are not due to thyroxin or di-iodo-tyrosin. Dogs were used as experimental animals.—Authors' Summary.

Tests of metabolism in patients with exophthalmic goiter: Self-regulation of diseased organism (Stoffwechsel-Untersuchungen bei morbus Basedowii; ein Beitrag zur Kenntnis der Selbstregubierung des erkrankten Köpers). Boenheim, F. Klin. Wchnschr. **9**: 497. 1930. Abst., J. A. M. A. **94**: 1879.

Boenheim determined the basal metabolic rate in 46 patients with exophthalmic goiter. He found that in 37 persons the basal metabolism was increased, in 6 it was normal and in 3 it was reduced. In order to show that in the latter 3 cases the diagnosis of exophthalmic goiter was correct, the author describes 2 of them. In these patients the condition of the basal metabolism and of the specific dynamic action indicates a sort of self-regulation on the part of the diseased organism. As yet it has not been determined what causes this self-regulation nor why it does not become effective in all instances. The author determined the basal metabolic rate and the specific dynamic action also in 10 patients with myxedema. In one patient the metabolic rate was normal, in all the others it was reduced. It was also noted that the specific dynamic action usually is inversely proportional to the basal metabolic rate; that is, the lower the basal metabolism, the higher the specific dynamic action.

Bacteriology of the thyroid in goitre. II. Some experimental results. Cantero, A. Canad. M. A. J. **22**: 343. 1930.

In a study of 110 cases of adenomatous goiter, with or without hyperthyroidism, a non-haemolyzing streptococcus was isolated in 58 cases, a Gram-positive diplococcus in 21, and an apparent diphtheroid bacillus closely related to the streptococcal group in 10 cases. The results are in agreement with those earlier published. Fresh experiments (123) on animals have been made with 37 different strains. It appears as if the thyroid gland in adenomatous goiter in man harbours partial tension organisms belonging to the streptococcal group which when injected intravenously into animals (rabbits) produce en-

largement and hyperaemia of the thyroid, liquefaction, and absorption of colloid, and in certain cases findings which are not obtained with streptococcal strains from ulcers and cholecystitis. The pathological changes are apparently not the result of active multiplication of the organisms. It appears that the thyroid is a favorable spot for lodgment of these strains resulting in the local production of a relatively large amount of toxic material.—A. T. C.

Operative mortality in hyperthyroidism. Clute, H. M. J. A. M. A. **95**: 389. 1930. Abst., A. M. A.

During a five-year interval, 2,128 patients were operated on for primary hyperthyroidism with fourteen deaths, a mortality rate of 0.65 per cent. In the same five years 641 patients with toxic adenomatous goiter were operated on with twelve deaths, a mortality rate of 1.87 per cent. The total number of patients during these five years who were operated on for hyperthyroidism is, therefore, 2,769. Of this number twenty-six died, a mortality rate for all patients with hyperthyroidism during the five-year interval of 0.93 per cent. Further reduction of the operative mortality in hyperthyroidism below its present low figure can be accomplished by the recognition of the fact that most unexpected mortality arises in patients (1) of 40 years and over; (2) weighing in the neighborhood of 100 pounds, or having large losses in weight and (3) having had well marked hyperthyroidism for more than a year. Thyroidectomy in these patients should in most instances be divided into stages, even though the patient's course on the table seems to warrant the complete procedure. By this arbitrary decision it is probable that a further reduction in mortality can be accomplished.

Disturbances in carbohydrate metabolism in exophthalmic goiter. Kugelmann, B. Klin. Wchnschr. **9**: 1533. 1930. Abst., J. A. M. A. **95**: 1386.

Kugelmann performed levulose tolerance tests on healthy persons and on patients with exophthalmic goiter. In the morning the blood sugar content was tested while the persons were still fasting. Then 100 gm. of levulose was administered and blood sugar tests were made first after fifteen-minute intervals and then after thirty-minute intervals. In healthy persons the blood sugar increases slightly but within two hours has again reached the normal level. In patients with exophthalmic goiter the increase is considerable and even three hours after the administration of the levulose the blood sugar is still much higher than normal. On the basis of his observations the author concludes that in the liver in thyrotoxicosis the glycogen depots are depleted, and the liver is no longer capable of changing large quantities of levulose into dextrose and of storing the dextrose. This demonstrates that in exophthalmic goiter there exists a functional disturbance of the liver, which becomes manifest in the pathologic behavior of the intermediate carbohydrate metabolism.

Comparative sensitivity to oxygen-want and to sodium lactate of the hearts of normal and thyroxinized animals. McEachern, D. and E. C. Andrus. Am. J. Physiol. **93**: 673. 1930.

The auricles of two rabbits were suspended side by side in a Dale bath. To one animal thyroxin had been administered in graduated doses over a period of two weeks. The authors have confirmed the observation of J. K. Lewis, that the spontaneous rhythm of the thyroxinized heart persists after isolation at a rate conspicuously more rapid than that of the normal. They have further shown: (1) That the auricles of the thyroxinized animals are far more sensitive to the withdrawal of oxygen than the normal. (2) That their rate and amplitude are depressed by doses of sodium lactate which produce little or no effect upon the normal auricles, and (3) that recovery from the above takes place more rapidly in the normal than in the thyroxinized auricles. The authors regard these results as indirect evidence of an accumulation of lactic acid in the heart of the thyroxinized rabbit.—Authors' Abst.

Pitfalls in the clinical application and interpretation of the basal metabolic rate. Rabinowitch, I. M. Canad. M. A. J. **23**: 152. 1930.

The various standards are dealt with critically. The seasonal, daily, and hourly fluctuations in individuals may amount to several per cent, and are not

the result of technical error. Muscular tone affects the result and a cold bath should never be allowed on the morning of the test. Muscular tone probably accounts for the tendency towards low metabolism exhibited by arthritics. Fever requires application of a correction, while following fever, especially when prolonged, the complication may arise of a lowered metabolism due to resulting exhaustion and undernutrition. Dietary habits affect the result. Heavy meat-eaters tend to have higher metabolic figures. The nervous factor must be watched. There may be an increased metabolism during the premenstrual period, and there is such an increase in the later months of pregnancy. Lactation, and involution of the uterus following pregnancy, cause a slight increase. The first effect of x-ray treatment is usually an increase of the rate. A particular individual may have a rate within the limits usually considered as normal, and yet, if his true normal figure be close to the lower "normal" limit, his actual figure may correspond with an existing hyperthyroidism.—A. T. C.

The effect of Lugol's solution on the metabolic rate of rabbits fed on abnormal human thyroid preparations. Reznichek, C. G. Am. J. Physiol. **93**: 683. 1930.

Studies were made of the effects upon the metabolic rates in rabbits by feeding abnormal human thyroid gland preparations with and without Lugol's solution. The following preparations were fed in varying daily doses: (1) Fresh hyperthyroid glands desiccated; obtained from the Wisconsin General Hospital, Madison. (2) Preserved (formalin) toxic adenoma and exophthalmic glands desiccated; obtained from and separated into the above grouping by the clinical staff of the Methodist Hospital, Madison. (3) Commercial desiccated thyroid of Lilly (control). The apparatus used for determining basal metabolism was an open circuit type using room air and determining (by weight) the CO_2 and O_2. The general laboratory average for normal rabbits was 2.61 calories per kilo per hour. Forty rabbits were used in this study. The normal metabolic rate for each was determined and desiccated gland was then fed in varying doses until a high level of metabolism was reached. All three of the above preparations acted alike in raising the metabolic rate 40 to 100 per cent above normal. Lugol's solution fed simultaneously in doses of 0.06 cc. daily did not protect the animal from an increase in metabolism. Lugol's solution fed alone caused no change in metabolism. Lugol's solution in doses of 0.06 cc. given to animals previously fed on any of the three thyroid preparations did not lower the metabolic rate.—Author's Abst.

The size of the heart in experimental hyperthyroidism. Simonds, J. P. and W. W. Brandes. Arch. Int. Med. **45**: 503. 1930.

Feeding 10 gm. of desiccated thyroid daily to healthy dogs can cause an actual hypertrophy of the heart. This hypertrophy is related to the loss of body weight, and occurs in those animals which have lost from approximately 25 per cent to 35 per cent of their original body weight. When the loss of weight exceeds approximately 35 per cent the heart loses the weight it has gained in hypertrophy and the heart weight-final body weight ratio approaches that seen in simple inanition. This hypertrophy involves all of the chambers of the heart with a slightly greater proportional increase in the left ventricle.
—Authors' Summary.

Prolonged treatment of exophthalmic goiter by iodine alone. Thompson, W. O., Phebe K. Thompson, A. G. Brailey and A. C. Cohen. Arch. Int. Med. **45**: 481. 1930.

Twenty-four patients with exophthalmic goiter (14 mild and 10 severe or moderately severe cases) were treated with iodine alone, either continuously or intermittently for periods ranging from one and one-half months to three years. The period of treatment was a year or more in 13 instances. With three exceptions (all unsatisfactory responses to iodine) the patients pursued their daily work throughout the period of observation, thus eliminating the effect of rest. In 9 of the 14 mild cases (64 per cent) the results were satisfactory; i.e., the clinical evidence of thyrotoxicosis was either completely or almost entirely kept under control, and the basal metabolism was kept at a normal level. In 4 of these 9 cases (in which iodine was omitted from 10 to

16 months) the disease has apparently disappeared, and in three others in which it was omitted from 4 to 17 weeks, there has been no recurrence of symptoms. In 3 of the 14 mild cases (22 per cent) the results were fairly satisfactory; i.e., there was definite improvement in spite of tardiness or fluctuations in the response. In two mild cases (14 per cent) the results were unsatisfactory; the disease did not become worse, however, on iodine. In the 10 severe or moderately severe cases, the results were satisfactory in one (10 per cent); there was no permanent satisfactory benefit in 4 (40 per cent); and the disease became worse in 5 (50 per cent).—Authors' Summary.

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ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION
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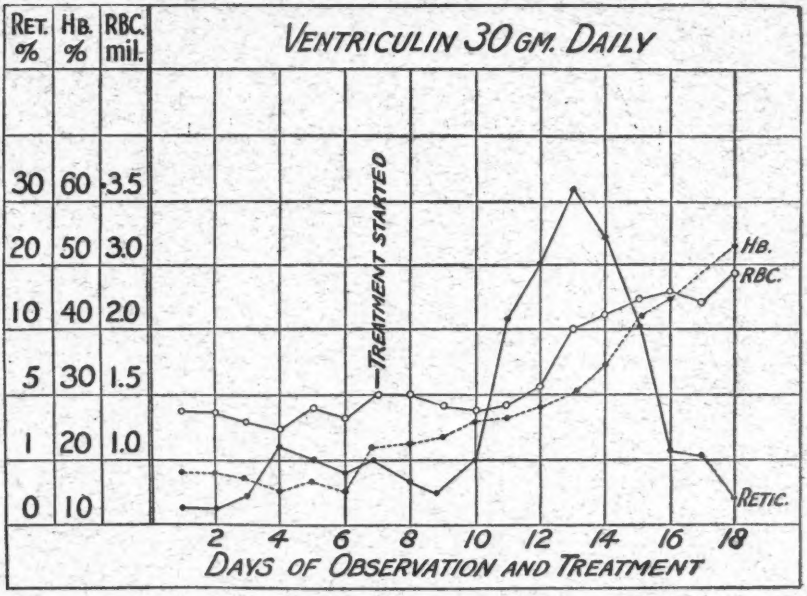

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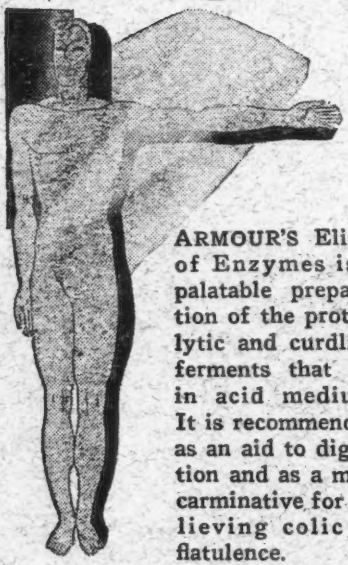

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